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ABSTRACT

This report offers a patient-based approach to lowering blood cholesterol levels which seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The goal is to establish criteria that define the candidates for medical intervention and to provide guidelines on how to detect, set goals for, treat, and monitor these patients over time. Information is given on: (1) classification, prevalence, detection, and evaluation of patients; (2) dietary treatment for lowering blood cholesterol; (3) monitoring and followup of diet; (4) dietary therapy for special groups; (5) approach to borderline-high blood cholesterol group; (6) when to consider drug therapy/treatment goals; (7) selection and use of drugs; (8) monitoring and followup of patients; and (9) adherance to drug therapy. Sixty references are included and appendices include tables of data on high blood cholesterol. (JD)

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Foreword

In agreeing to serve on the Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults, the members of this Panel accepted a unique and ambitious task. They were charged to consider the available evidence on coronary heart disease and high blood cholesterol, identify pertinent issues, and make recommendations to physicians and other health professionals.

Under Dr. DeWitt S. Goodman's leadership, the Panel met this significant challenge. Its report not only builds upon, but moves beyond, the work of the *1984 Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease* to reflect the current state of knowledge about cholesterol and coronary heart disease. It provides new and detailed recommendations for treating high blood cholesterol in adults and addresses two basic questions: *Who should be treated, and how should they be treated?*

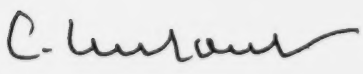
The report is organized into three main areas and includes recommendations for:

- Classifying patients based on total and low density lipoprotein cholesterol.
- Treating patients with diet alone.
- Treating patients with drugs in addition to diet.

It also addresses patient counseling issues and the management of special patient and population groups.

In developing the report, the Panel followed two basic principles. *One was simplicity—to make the guidelines as simple as possible. The second principle was to provide enough detail to assist physicians and health care professionals in dealing with individual patients.*

I believe that these recommendations, the first major report issued by the National Cholesterol Education Program, are likely to have a great influence on the way high blood cholesterol is treated. If these recommendations are adopted in the way we hope and expect, they will have a significant effect on reducing the development of premature coronary heart disease in this country and internationally.



Claude Lenfant, M.D.
Director
National Heart, Lung, and Blood Institute
National Institutes of Health
and
Chairman
National Cholesterol Education Program
Coordinating Committee

Expert Panel on Detection, Evaluation, and Treatment of High Blood Cholesterol in Adults

Panel Chairman

DeWitt S. Goodman, M.D.
Professor of Medicine
Columbia University
College of Physicians and Surgeons
New York, NY

Prevalence, Detection, Diagnosis, and Evaluation Subcommittee

Stephen B. Hulley, M.D., M.P.H., Chairman
Director, Clinical Epidemiology Program
San Francisco General Hospital
San Francisco, CA

Luther T. Clark, M.D.
Associate Director
Kings County Hospital Center
State University of New York
Health Science Center at Brooklyn
Brooklyn, NY

C.E. Davis, Ph.D.
Deputy Director, Collaborative Studies Coordinating Center
Professor, Department of Biostatistics
University of North Carolina
Chapel Hill, NC

Valentin Fuster, M.D.
Professor of Medicine
Division of Cardiology
Mount Sinai School of Medicine
New York, NY

John C. LaRosa, M.D.
Dean for Clinical Affairs
George Washington University
School of Medicine
Washington, DC

Albert Oberman, M.D.
Professor and Director
Division of General and Preventive Medicine
School of Medicine
The University of Alabama in Birmingham
Birmingham, AL

Ernst J. Schaefer, M.D.
Chief, Lipid Metabolism Laboratory
Associate Professor of Medicine
USDA Human Nutrition Research Center on Aging at Tufts University and New England Medical Center
Boston, MA

Daniel Steinberg, M.D., Ph.D.
Professor of Medicine
Division of Endocrinology and Metabolism
Department of Medicine
University of California, San Diego
La Jolla, CA

Dietary Treatment Subcommittee

W. Virgil Brown, M.D., Co-Chairman
President
Medlantic Research Foundation
Washington, DC

Scott M. Grundy, M.D., Ph.D., Co-Chairman
Director, Center for Human Nutrition
University of Texas Health Science Center
Dallas, TX

Diane M. Becker, Sc.D., M.P.H.
Assistant Professor of Medicine
Co-Director, Preventive Cardiology Programs
The Johns Hopkins Hospital
Baltimore, MD

Edwin L. Bierman, M.D.
Professor of Medicine
Division of Metabolism, Endocrinology, and Nutrition
University of Washington
Seattle, WA

Jacqueline Sooter-Bochenek, R.D., M.S.
Director, Clinical Nutrition
University of California, San Diego Medical Center
San Diego, CA

Rebecca M. Mullis, Ph.D., R.D.
Assistant Professor
University of Minnesota
Division of Epidemiology
School of Public Health
Minneapolis, MN

Neil Stone, M.D.
Associate Professor of Medicine
Northwestern University Medical School
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Drug Treatment Subcommittee

Donald B. Hunninghake, M.D., Chairman
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Minneapolis, MN

Jacqueline M. Dunbar, R.N., Ph.D.
Director of Nursing
Western Psychiatric Institute and Clinic
Pittsburgh, PA

Henry N. Ginsberg, M.D.
Associate Professor of Medicine
Columbia University
College of Physicians and Surgeons
New York, NY

D. Roger Illingworth, M.D., Ph.D.
Associate Professor of Medicine
Division of Endocrinology, Metabolism,
and Clinical Nutrition
The Oregon Health Sciences University
Portland, OR

Harold C. Sadin, M.D.
Washington, D C

Gustav Schonfeld, M.D.
Director, Lipid Research Clinic
Washington University School of Medicine
St. Louis, MO

Executive Director of the Panel

James I. Cleeman, M.D.
Coordinator
National Cholesterol Education Program
Office of Prevention, Education, and Control
National Heart, Lung, and Blood Institute
Bethesda, MD

Ex-Officio Members

H. Bryan Brewer, Jr., M.D.
Chief, Molecular Disease Branch
National Heart, Lung, and Blood Institute
Bethesda, MD

Nancy Ernst, M.S., R.D.
Nutrition Coordinator
National Heart, Lung, and Blood Institute
Bethesda, MD

William T. Friedewald, M.D.
Associate Director for Disease Prevention
National Institutes of Health
Bethesda, MD

Jeffrey M. Hoeg, M.D.
Senior Investigator
Molecular Disease Branch
National Heart, Lung, and Blood Institute
Bethesda, MD

Basil Rifkind, M.D.
Chief, Lipid Metabolism-Atherogenesis Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
Bethesda, MD

Consultant

David Gordon, M.D., Ph.D.
Medical Officer
Lipid Metabolism-Atherogenesis Branch
Division of Heart and Vascular Diseases
National Heart, Lung, and Blood Institute
Bethesda, MD

Staff

Barbara Duvekot, M.P.H., R.D.

Marguerite A. Evans, M.S., R.D.

Anne Lipscomb, M.P.H.

Member Organizations

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Increased blood cholesterol levels, more specifically increased levels of LDL-cholesterol, are causally related to an increased risk of coronary heart disease (CHD). Coronary risk rises progressively with cholesterol level, particularly when cholesterol levels rise above 200 mg/dl. There is also substantial evidence that lowering total and LDL-cholesterol levels will reduce the incidence of CHD.

Two approaches can be used to lower blood cholesterol levels. The first is the subject of this report: a patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The goal here is to establish criteria that define the candidates for medical intervention and to provide guidelines on how to detect, set goals for, treat, and monitor these patients over time. The second approach, the population (public health) strategy, aims to shift the distribution of cholesterol levels in the entire population to a lower range. These two approaches are complementary and, together, represent a coordinated strategy aimed at reducing cholesterol levels and coronary risk.

Case Finding: Initial Classification by Total Blood Cholesterol

Serum total cholesterol should be measured in all adults 20 years of age and over at least once every 5 years; this measurement may be made in the nonfasting state. Levels below 200 mg/dl are classified as "desirable blood cholesterol," those 200 to 239 mg/dl as "borderline-high blood cholesterol," and those 240 mg/dl and above as "high blood cholesterol." The cutpoint that defines high blood cholesterol (240 mg/dl) is a value above which risk of CHD rises steeply, and corresponds approximately to the 75th percentile for the adult U.S. population. The cutpoints recommended in this report are uniform for adult men and women of all ages.

Along with cholesterol testing, all adults should also be evaluated for the presence of other CHD risk factors, including hypertension, cigarette smoking, diabetes mellitus, severe obesity, and a history of CHD in the patient or of premature CHD in family members. Patients with other risk factors should be given other forms of preventive care as appropriate.

Patients with desirable blood cholesterol levels ($<$200 mg/dl) should be given general dietary and risk reduction educational materials, and advised to have another serum cholesterol test within 5 years. Patients with cholesterol levels 200 mg/dl or greater should have the value confirmed by repeating the test; the average of the two test results is then used to guide subsequent decisions. Patients with high blood cholesterol ($\geq$240 mg/dl) should undergo lipoprotein analysis, as should those with borderline-high blood cholesterol (200-239 mg/dl) who are at high risk because they have definite CHD or two other CHD risk factors; in this report male sex is considered a risk factor for the purpose of estimating risk status. Patients with confirmed borderline-high blood cholesterol levels who do not have CHD or two other risk factors do not need further evaluation and active medical

therapy; they should be given the dietary information designed for the general population and reevaluated at 1 year.

Some experts believe that patients in the borderline-high blood cholesterol group who have one other risk factor (e.g., hypertension) or are of younger age (20-39 years) should also undergo lipoprotein analysis. Although this is not recommended here as a general approach for the borderline-high blood cholesterol group, it is clear that individualized clinical judgment and patient management is appropriate for this group.

Initial Classification and Recommended Followup
Based on Total Cholesterol

A. Classification

< 200 mg/dl	Desirable Blood Cholesterol
200-239 mg/dl	Borderline-High Blood Cholesterol
≥ 240 mg/dl	High Blood Cholesterol

B. Recommended Followup

Total Cholesterol < 200 mg/dl	Repeat within 5 years
Total Cholesterol 200-239 mg/dl	
Without definite CHD or two other CHD risk factors (one of which can be male sex)	Dietary information and recheck annually
With definite CHD or two other CHD risk factors (one of which can be male sex)	Lipoprotein analysis; further action based on LDL-cholesterol level
Total Cholesterol ≥ 240 mg/dl	

Deciding to Treat: Classification by LDL-Cholesterol

Once someone is identified as requiring lipoprotein analysis, the focus of attention should shift from total cholesterol to LDL-cholesterol. The ultimate objective of case finding and screening is to identify individuals with elevated LDL-cholesterol levels. Similarly, the specific goal of treatment is to lower LDL-cholesterol levels. Hence the level of LDL-cholesterol will serve as the key index for clinical decision making about cholesterol-lowering therapy.

Lipoprotein analysis involves measurement of the fasting levels of total cholesterol, total triglyceride, and HDL-cholesterol. From these values, LDL-cholesterol is calculated as follows:

LDL-cholesterol = total cholesterol − HDL-cholesterol − (triglyceride/5).

Levels of LDL-cholesterol of 160 mg/dl or greater are classified as "high-risk LDL-cholesterol," and those 130-159 mg/dl as "borderline-high-risk LDL-cholesterol." Patients with high-risk LDL-cholesterol levels, and those with borderline-high-risk LDL-cholesterol who have definite CHD or two other risk factors (one of which can be male sex), should have a complete clinical evaluation and then begin cholesterol-lowering treatment. A basic principle adopted in this report is that the presence of other risk factors or definite CHD warrants initiating treatment at lower LDL-cholesterol levels and the setting of lower LDL-cholesterol treatment goals. In this scheme, a low level of HDL-cholesterol (below 35 mg/dl) is considered another risk factor (like hypertension) that will affect the assessment of overall coronary risk, and in this way influence clinical decisions about treatment.

The clinical evaluation should include a complete history, physical examination, and basic laboratory tests. This workup will aim to determine whether the high LDL-cholesterol level is secondary to another disease or a drug, and whether or not a familial lipid disorder is present. The patient's total coronary risk and clinical status, as well as age and sex, should be considered in developing a cholesterol-lowering treatment program.

Classification and Treatment Decisions Based on LDL-Cholesterol

A. Classification

< 130 mg/dl	Desirable LDL-Cholesterol
130-159 mg/dl	Borderline-High-Risk LDL-Cholesterol
≥ 160 mg/dl	High-Risk LDL-Cholesterol

B. Dietary Treatment

	Initiation Level	Minimal Goal
Without CHD or two other risk factors*	≥ 160 mg/dl	< 160 mg/dl§
With CHD or two other risk factors*	≥ 130 mg/dl	< 130 mg/dl#

C. Drug Treatment

	Initiation Level	Minimal Goal
Without CHD or two other risk factors*	≥ 190 mg/dl	< 160 mg/dl
With CHD or two other risk factors*	≥ 160 mg/dl	< 130 mg/dl

* Patients have a lower initiation level and goal if they are at high risk because they already have definite CHD, or because they have any two of the following risk factors: male sex, family history of premature CHD, cigarette smoking, hypertension, low HDL-cholesterol, diabetes mellitus, definite cerebrovascular or peripheral vascular disease, or severe obesity.

§/# Roughly equivalent to total cholesterol < 240 mg/dl (§) or < 200 mg/dl (#) as goals for monitoring dietary treatment.

Dietary Treatment

Treatment begins with dietary therapy. The minimal goals of therapy are to lower LDL-cholesterol to levels below the cutpoints for initiating therapy, i.e., to below 160 mg/dl, or to below 130 mg/dl if definite CHD or two other CHD risk factors are present. Ideally, even lower levels of LDL-cholesterol should be attained, if possible, to achieve a further reduction in risk.

Although the goal of therapy is to lower LDL-cholesterol, most patients can be managed during dietary therapy on the basis of their total cholesterol levels. This has the advantage of avoiding the additional costs and the need for fasting blood involved in the measurement of LDL-cholesterol levels. Serum total cholesterol levels of 240 and 200 mg/dl correspond roughly to LDL-cholesterol levels of 160 and 130 mg/dl, respectively. Thus, the monitoring goals during dietary therapy are to lower serum total cholesterol level to below 240 mg/dl for patients with an LDL-cholesterol goal of <160 mg/dl, or to below 200 mg/dl for patients with an LDL-cholesterol goal of <130 mg/dl.

The general aim of dietary therapy is to reduce elevated cholesterol levels while maintaining a nutritionally adequate eating pattern. Dietary therapy should occur in two steps, the Step-One and Step-Two Diets, that are designed to progressively reduce intakes of saturated fatty acids and cholesterol, and to promote weight loss in patients who are overweight by eliminating excess total calories. The Step-One Diet should be prescribed and explained by the physician and his or her staff. This diet involves an intake of total fat less than 30% of calories, saturated fatty acids less than 10% of calories, and cholesterol less than 300 mg/day. The Step-Two Diet, used if the response to the Step-One Diet is insufficient, calls for a further reduction in saturated fatty acid intake to less than 7% of calories and in cholesterol to less than 200 mg/day. The Step-One Diet calls for the reduction of the major and obvious sources of saturated fatty acids and cholesterol in the diet; for many patients this can be achieved without a radical alteration in dietary habits. The Step-Two Diet requires careful attention to the whole diet so as to reduce intake of saturated fatty acids and cholesterol to a minimal level compatible with an acceptable and nutritious diet. Involvement of a registered dietitian is very useful, particularly for intensive dietary therapy such as the Step-Two Diet.

After starting the Step-One Diet, the serum total cholesterol level should be measured and adherence to the diet assessed at 4-6 weeks and at 3 months. If the total cholesterol monitoring goal is met, then the LDL-cholesterol level should be measured to confirm that the LDL goal has been achieved. If this is the case, the patient enters a long-term monitoring program, and is seen quarterly for the first year and twice yearly thereafter. At these visits total cholesterol levels should be measured, and dietary and behavior modifications reinforced.

If the cholesterol goal has not been achieved with the Step-One Diet, the patient should generally be referred to a registered dietitian. With the aid of the dietitian, the patient should progress to the Step-Two Diet, or to another trial on the Step-

One Diet (with progression to the Step-Two Diet if the response is still not satisfactory). On the Step-Two Diet, total cholesterol levels should again be measured and adherence to the diet assessed after 4-6 weeks and at 3 months of therapy. If the desired goal for total cholesterol (and for LDL-cholesterol) lowering has been attained, long-term monitoring can begin. If not, drug therapy should be considered. A minimum of 6 months of intensive dietary therapy and counseling should usually be carried out before initiating drug therapy; shorter periods can be considered in patients with severe elevations of LDL-cholesterol (>225 mg/dl) or with definite CHD. Drug therapy should be added to dietary therapy, and not substituted for it.

Drug Treatment

Drug therapy should be considered for an adult patient who, despite dietary therapy, has an LDL-cholesterol level of 190 mg/dl or higher if the patient does not have definite CHD or two other risk factors (one of which can be male sex). If the patient does have definite CHD or two other risk factors, then drug therapy should be considered at LDL-cholesterol levels of 160 mg/dl or higher. The goals of drug therapy are the same as those of dietary therapy: to lower LDL-cholesterol to below 160 mg/dl, or to below 130 mg/dl if definite CHD or two other risk factors are present. These are minimal goals; if possible, considerably lower levels of LDL-cholesterol should be attained.

Individualized clinical judgment is needed for patients who do not meet these criteria for drug therapy, but have not attained their minimal goals on dietary therapy. These patients include those without definite CHD or two other risk factors whose LDL-cholesterol levels remain in the range of 160-190 mg/dl, and patients with CHD or two other risk factors in the range of 130-160 mg/dl, on adequate dietary therapy. In general, maximal efforts should be made in this group to achieve lower cholesterol levels and lower CHD risk by means of nonpharmacologic approaches. Consideration should also be given to the use of low doses of bile acid sequestrants in these patients, especially in males. Moreover, many experts feel that patients with definite CHD should receive drug therapy if their minimal LDL-cholesterol goal (<130 mg/dl) has not been reached.

The drugs of first choice are the bile acid sequestrants (cholestyramine, colestipol) and nicotinic acid. Both cholestyramine and nicotinic acid have been shown to lower CHD risk in clinical trials, and their long-term safety has been established. However, these drugs require considerable patient education to achieve effective adherence. Nicotinic acid is the preferred drug in patients with concurrent hypertriglyceridemia (triglycerides ≥250 mg/dl), because bile acid sequestrants tend to increase triglyceride levels.

A new class of drugs, to be considered after the bile acid sequestrants and nicotinic acid, is the HMG CoA reductase inhibitors (e.g., lovastatin). These drugs are very effective in lowering LDL-cholesterol levels, but their effects on CHD incidence and their long-term safety have not yet been established.

Other available drugs include gemfibrozil, probucol, and clofibrate. Gemfibrozil and clofibrate are fibric acid derivatives; they are primarily effective for lowering elevated triglyceride levels, but are not FDA approved for routine use in lowering cholesterol.

After starting drug therapy, the LDL-cholesterol level should be measured at 4-6 weeks, and then again at 3 months. If the response to drug therapy is adequate (i.e., the LDL-cholesterol goal has been achieved), then the patient should be seen every 4 months, or more frequently when drugs requiring closer followup are used, in order to monitor the cholesterol response and possible side effects of therapy. For long-term monitoring, serum total cholesterol alone can be measured at most follow-up visits, with lipoprotein analysis (and LDL-cholesterol estimation) carried out once a year.

If the response to initial drug therapy is not adequate, the patient should be switched to another drug, or to a combination of two drugs. The combination of a bile acid sequestrant with either nicotinic acid or an HMG CoA reductase inhibitor has the potential of lowering LDL-cholesterol levels by 40-50% or more. The combination of colestipol and nicotinic acid has been shown to beneficially influence coronary atherosclerotic lesions. For most patients, the judicious use of one or two drugs should be able to provide an adequate LDL-cholesterol-lowering effect.

Drug therapy is likely to continue for many years or for a lifetime. Hence, the decision to add drug therapy to the regimen should be made only after vigorous efforts at dietary treatment have not proven sufficient. The patient must be well informed about the goals and side effects of medication and the need for long-term commitment. In the ideal treatment setting, the management of high-risk cholesterol levels would call on the expertise of a variety of professionals. The office nurse or physician's assistant can help greatly in promoting adherence to dietary and drug therapy. A registered dietitian can be of great value in dietary therapy. The pharmacist can help to provide counseling and promote adherence with drug therapy. Consultation with a lipid specialist is useful for patients with unusually severe, complex, or refractory lipid disorders.

A. Background and Introduction

This report provides practical guidelines for clinicians to use in measuring and reducing blood cholesterol in adult patients.* The report adds a more specific set of recommendations to basic policies set forth by previous bodies, notably the National Institutes of Health Consensus Development Conference on Lowering Blood Cholesterol to Prevent Heart Disease (1). While it is recognized that approaches for modifying the cholesterol levels in whole population groups are important, this report focuses on caring for individual patients.

1. *Basic Description of Lipids and Lipoproteins.*

Cholesterol is a fat-like substance (lipid) that is a key component of cell membranes and a precursor of bile acids and steroid hormones. Cholesterol travels in the circulation in spherical particles containing both lipids and proteins called lipoproteins. The cholesterol level in blood plasma is determined partly by inheritance and partly by the fat and cholesterol content of the diet. Other factors such as obesity and physical inactivity may also play a role.

Three major classes of lipoproteins can be measured in the serum of a fasting individual: very low density lipoproteins (VLDL), low density lipoproteins (LDL), and high density lipoproteins (HDL). The LDL are the major atherogenic class, and typically contain 60-70% of the total serum cholesterol. The HDL usually contain 20-30% of the total cholesterol, and their levels are inversely correlated with risk for coronary heart disease (CHD). The VLDL, which are largely composed of triglyceride, contain 10-15% of the total serum cholesterol.

Because most of the cholesterol in the serum is found in the LDL, the concentration of total cholesterol is closely correlated with the concentration of LDL-cholesterol. Thus, while LDL-cholesterol is the actual target of cholesterol-lowering efforts, total cholesterol can be used in its place in the initial stages of evaluating a patient's serum lipids. Testing for serum total cholesterol is more available and less expensive and does not require that the patient be fasting. On the other hand, LDL-cholesterol offers more precision as a risk factor and is therefore preferred for clinical decisions about interventions to lower blood cholesterol, especially in patients who may be candidates for cholesterol-lowering drugs.

2. *Rationale for Intervention.*

a. The evidence that LDL-cholesterol is a cause of CHD.

The conclusion that high levels of LDL-cholesterol are a cause of coronary atherosclerosis and produce an increased risk of CHD comes from the congruent results of many studies.

*This report addresses patients 20 years of age and above; a separate panel will provide guidelines for children and adolescents.

- **Epidemiologic evidence**: A large body of epidemiologic evidence supports a direct relationship between the level of serum total and LDL-cholesterol and the rate of CHD (2,3,4). Comparisons among various populations throughout the world reveal a direct correlation between serum cholesterol levels and CHD rates. People who have migrated to a country that has a higher average serum cholesterol level gradually acquire the dietary habits, serum cholesterol level, and CHD rates of their new country. Prospective studies of the individuals within a population have uniformly shown that serum cholesterol levels predict the future occurrence of CHD morbidity and mortality. This association is continuous throughout the range of cholesterol levels in the population (Figure 1) (5,6). At higher levels of serum cholesterol the relationship becomes particularly strong. For persons with cholesterol values in the top 10% of the population distribution, the risk of CHD mortality is four times as high as the risk in the bottom 10% of the population.

FIGURE 1. — *Relationship of serum cholesterol to CHD death in 361,662 men age 35-57 during an average followup of 6 years. Each point represents the median value for 5% of the population (5).*

- **Genetic and physiologic evidence**: Premature CHD can result from high LDL-cholesterol levels even in the absence of any other risk factors (7). This is most clearly demonstrated in children who have the rare homozygous familial hypercholesterolemia, a disorder characterized by the absence of the specific cell-surface receptors that normally remove LDL from the circulation (8). LDL-cholesterol levels can be as high as 1,000 mg/dl, and severe atherosclerosis and CHD can develop during the first 2 decades of life. Patients with the more common heterozygous form of familial hypercholesterolemia and partial deficiencies of LDL-receptor function commonly develop premature CHD in the middle decades of life.
- **Animal model evidence**: Animal models have demonstrated important relationships between LDL-cholesterol and atherosclerosis (9). Many animal species (including monkeys and baboons) develop atherosclerosis when fed diets that raise their serum cholesterol levels. These hypercholesterolemic animals develop intimal lesions that progress from fatty streaks to complicated ulcerated plaques resembling those of human atherosclerosis. Severe atherosclerosis in monkeys regresses when the blood cholesterol is lowered substantially for an extended period by diet or drugs. These studies thus support a causal relationship between LDL-cholesterol and atherosclerosis, and suggest that this process may be reversible under some circumstances.

b. The evidence that reducing LDL-cholesterol levels will prevent CHD.

The evidence noted above from epidemiologic, genetic, and animal investigations strongly supports a causal link between elevated serum cholesterol levels and CHD. In addition, clinical trials have shown that this risk can be altered—that lowering LDL-cholesterol in men with high levels decreases the incidence of CHD.

The issue of whether lowering LDL-cholesterol levels by dietary and drug interventions can reduce the incidence of CHD has been addressed in more than a dozen randomized clinical trials. One of the largest, the Coronary Primary Prevention Trial, which compared the cholesterol-lowering drug cholestyramine with a placebo, produced statistically significant reductions in LDL-cholesterol levels and in the incidence of CHD (10). An aggregate analysis that pools the results of serum cholesterol-lowering trials confirms an effect on CHD incidence. Moreover, the Coronary Drug Project has shown a significant decrease in overall mortality (compared with the placebo group) in a long-term followup of men treated with nicotinic acid after myocardial infarction (11). In addition, a recent angiographic study showed that cholesterol-lowering dietary and drug therapy slowed the progression and produced regression of coronary atherosclerosis in men with bypass grafts (12).

In summary, these findings support the conclusion that lowering total and LDL-cholesterol levels will reduce the subsequent incidence of CHD events. Moreover, the pooled analysis of clinical trial findings suggests that intervention is as effective in secondary prevention (preventing recurrent myocardial infarction and death in patients who have had a heart attack) as it is in primary prevention. The direct

evidence from clinical trials is strongest in middle-aged men with high initial cholesterol levels. However, the complete set of evidence, including the epidemiologic observations and animal experiments, strongly supports the generalization that reducing total and LDL-cholesterol levels is also likely to reduce CHD incidence in younger and older men, in women, and in individuals with more moderate elevations of cholesterol.

c. The magnitude of the reduction in CHD.

Epidemiologic studies and clinical trials are remarkably consistent in supporting the projection that for individuals with serum cholesterol levels initially in the 250-300 mg/dl (6.5-7.8 mmol/L) range, each 1% reduction in serum cholesterol level yields approximately a 2% reduction in CHD rates (13). Thus, for example, it is reasonable to estimate that a 10-15% reduction in serum cholesterol level resulting from the diets recommended in this report should reduce CHD risk by 20-30%.

The *absolute magnitude* of these benefits will probably be greatest in patients who are at high risk because of the presence of other risk factors, such as cigarette smoking and hypertension. This concept is illustrated in Table 1 using data from the Multiple Risk Factor Intervention Trial (MRFIT). Among nonsmokers with normal blood pressure, the risk of CHD death per 1,000 men in the 6 years of observation was 6.4 in the top quintile of serum cholesterol and 1.6 in the bottom quintile, a difference of 4.8. Among smokers with hypertension, the comparable figures were 21.4 and 6.3, a difference of 15.1. Thus, an intervention that lowered cholesterol levels from the highest to the lowest quintile should have three times the benefit (15 versus 5 deaths prevented per thousand persons) when applied to men who have the other two risk factors (assuming no change in those other risk factors). These risk relationships are the basis for recommending lower cholesterol cutpoints and goals for treating patients who for other reasons (in addition to cholesterol) are at high risk for developing CHD.

TABLE 1. — *CHD deaths/1,000 in men age 35-57 with an average followup of 6 years according to serum cholesterol quintile and presence or absence of other risk factors (14)*

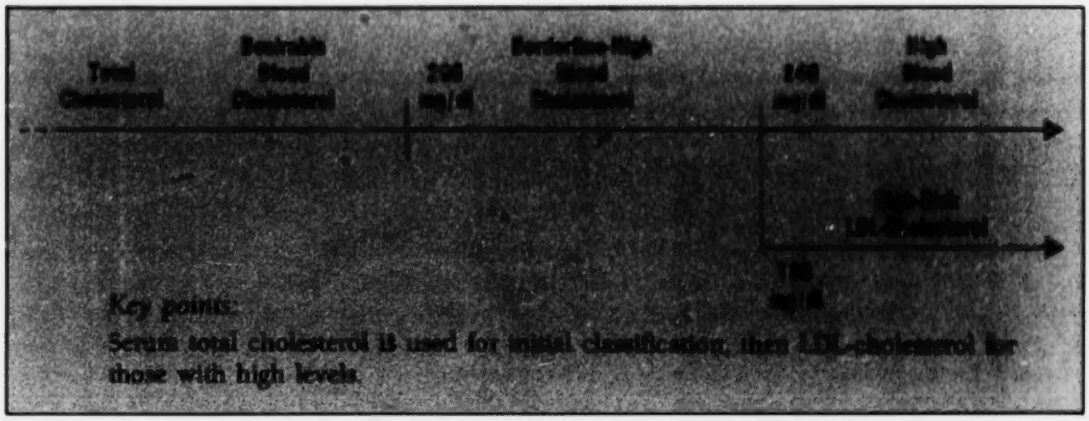
Serum Cholesterol Quintile, mg/dl	Normotensive Nonsmoker	Hypertensive Smoker
<193	1.6	6.3
193-213	2.3	10.8
214-234	2.7	15.5
235-264	3.8	16.8
>264	6.4	21.4

Key point:

The difference in absolute risk in the highest versus the lowest quintile of serum cholesterol is greater in patients who are at high risk for other reasons.

FIGURE

2. — *Classification by total and LDL-cholesterol levels*


Key points:
Serum total cholesterol is used for initial classification, then LDL-cholesterol for those with high levels.

3. *Classification of Patients by Total and LDL-Cholesterol Levels.*[§]

The classification system (Figure 2) begins with measurement of the total cholesterol level. Serum is most frequently used for this measurement, and cholesterol levels in this report are stated as serum values.[#] Levels below 200 mg/dl are classified as "desirable blood cholesterol," those 200-239 mg/dl (5.2-6.2 mmol/L) as "borderline-high blood cholesterol," and those 240 mg/dl (6.2 mmol/L) and above (corresponding to approximately the top 25% of the entire adult population 20 years of age and above) as "high blood cholesterol."

Patients with high blood cholesterol need additional evaluation and are further classified for the purposes of clinical decisions about possible dietary and drug treatment by performing lipoprotein analysis and estimating the more specific determinant of CHD risk, the LDL-cholesterol level. Levels of LDL-cholesterol that are 160 mg/dl (4.1 mmol/L) and above are classified as "high-risk LDL-cholesterol."

Because the relationship between serum cholesterol level and CHD is a continuous and steadily increasing one (Figure 1), these cutpoints are necessarily somewhat arbitrary. However, this is also true of other risk factors, such as blood pressure, and the success of basing clinical decisions on whether or not a patient is classified as hypertensive indicates the value of establishing cutpoints for clinical decisions. The 240 mg/dl cutpoint for total serum cholesterol is a level at which CHD risk is almost double that at 200 mg/dl and is rising steeply. Patients with cholesterol levels at or above this cutpoint have sufficiently high risk to warrant more detailed evaluation and possible treatment.

[§] Population distributions for serum total cholesterol and LDL-cholesterol levels in the United States are provided in Appendix I. To convert serum values to plasma, multiply by 0.97. To convert cholesterol values in mg/dl to millimoles per liter, multiply by 0.02586. To convert triglyceride values in mg/dl to millimoles per liter, multiply by 0.01129.

[#] Cholesterol levels can also be measured on plasma. If, as is customary, EDTA is used as an anticoagulant, the results should be multiplied by 1.03 to arrive at the serum equivalent.

4. *Other Risk Factors for CHD.*

CHD is a disease of multifactorial etiology, and other risk factors should also be considered in preventive medical efforts. These include modifiable factors like hypertension and cigarette smoking, which are appropriate targets for intervention efforts.¶ Everyone tested for blood cholesterol should also be examined for other risk factors (see Table 2, page 23), and interventions should be undertaken as appropriate. All patients should receive educational materials that describe general dietary and lifestyle approaches to reducing the risk of CHD.** Advice to quit smoking is particularly important because it has the potential not only to reduce CHD risk by 50%, but also to prevent cancer and chronic lung disease.

In addition to being candidates for intervention, these modifiable factors increase the absolute level of CHD risk and thereby enhance the potential value of reducing cholesterol levels. This is also true for the fixed risk factors like older age, male sex, family history of premature CHD, and CHD in the patient. Two other lipid and lipoprotein factors that have a bearing on CHD, HDL-cholesterol and triglyceride, are not dealt with in this report as direct targets for intervention but enter into clinical decisions in ways that are discussed in the sections that follow and in Appendix II.

5. *The Patient-Based Approach and the Population-Based Approach.*

The 1984 Consensus Development Conference and other groups have recommended two major strategies for preventing CHD by lowering blood cholesterol (1,15). One is the subject of this report: a patient-based approach that seeks to identify individuals at high risk who will benefit from intensive intervention efforts. The goal here is to establish total and LDL-cholesterol cutpoints that define the candidates for medical intervention, and to provide guidelines on how to detect, set goals for, treat, and monitor these patients over time.

The other strategy is the population-based approach that seeks to lower the mean serum cholesterol level by modifying the dietary habits of the entire population. This strategy has the general goal of lowering the serum cholesterol levels of the population at large.

These two strategies are complementary, not competitive, and the National Cholesterol Education Program is considering both in the development of its activities. This report is the product of an expert panel focused on the patient-based approach. Another panel is charged with examining the scientific evidence and making recommendations for the population-based approach.

¶ Assistance in intervention efforts aimed at hypertension and cigarette smoking may be obtained from two National Heart, Lung, and Blood Institute publications: "The 1984 Report of the Joint National Committee on Detection, Evaluation, and Treatment of High Blood Pressure" (to be updated in 1988); and "Clinical Opportunities for Smoking Intervention—A Guide for the Busy Physician."

**These may be obtained from a variety of sources—see the list in the National Cholesterol Education Program publication "Cholesterol Resources for the Physician."

6. *The Importance of a Multidisciplinary Team Approach.*

This report presents guidelines for interventions that are partly the responsibility of the physicians, dietitians, nurses, pharmacists, and other health professionals who must work together as a team to decide on the best approach for testing and treating each patient, and for implementing and following up these recommendations. The interventions are also the responsibility of the patient, for whom the challenge is to make the dietary and other lifestyle changes that are needed for successful reduction of CHD risk.

B. Detection and Evaluation

1. *Who Should Be Tested.*

The total cholesterol level should be measured in all adults 20 years of age and over at least once every 5 years. Although screening programs that have the specific purpose of inviting the public to receive this test can be used (provided that care is taken to assure that the screening determination is accurate and that there is appropriate followup for further tests and treatment), the usual approach is through case finding. Case finding is defined as testing the cholesterol level as part of any medical examination.

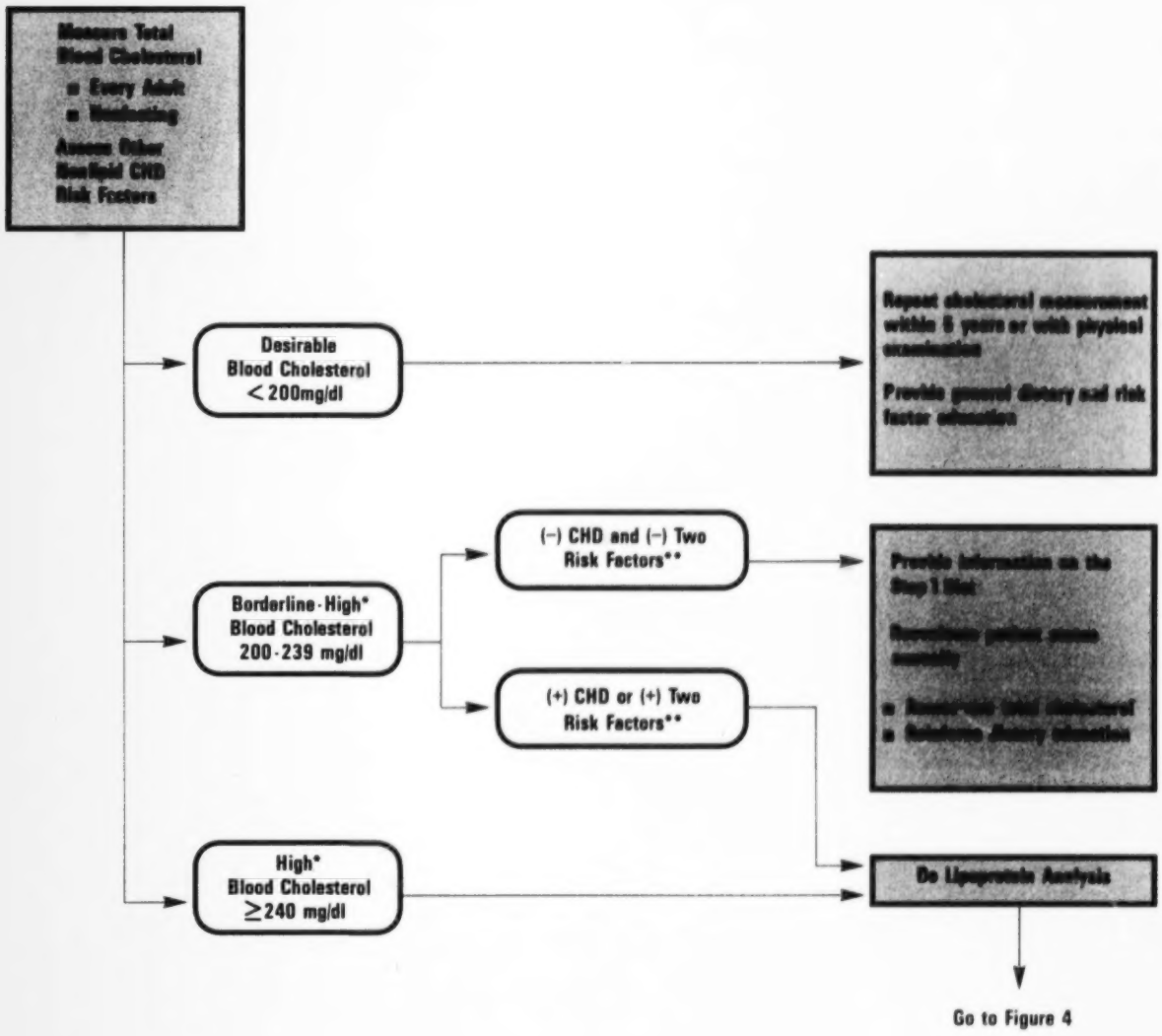
2. *Classification of Patients.*

a. Initial classification based on **Total Cholesterol** *level.*

The schedule for evaluation and followup of serum cholesterol is shown in Figure 3. The schedule begins with measurement of nonfasting serum total cholesterol and an assessment of other nonlipid risk factors including blood pressure, smoking, and history of CHD in the patient or of premature CHD in family members. The presence of a high cholesterol level is confirmed with a second test and then fasting LDL-cholesterol is measured in order to provide a more precise estimate of risk on which to base treatment. Patients should be asked not to change their eating habits during this series of baseline tests.

Patients with a *desirable blood cholesterol* level at this initial test (<200 mg/dl) should be given advice and educational materials on the diet recommended for the general population and advised to have another serum cholesterol test within 5 years. As with all patients, these individuals should also have been evaluated for hypertension, cigarette smoking, and other risk factors, and should be given other forms of preventive medical care as appropriate.

FIGURE
3 — Initial Classification Based on Total Cholesterol


Measure Total Blood Cholesterol
Desirable Blood Cholesterol < 200mg/dl
Borderline-High* Blood Cholesterol 200-239 mg/dl
(−) CHD and (−) Two Risk Factors**
(+) CHD or (+) Two Risk Factors**
High* Blood Cholesterol ≥240 mg/dl
Do Lipoprotein Analysis
Go to Figure 4

*Must be confirmed by repeat measurement; use average value.
**One of which can be male sex (see Table 2).

Patients with a serum cholesterol of 200 mg/dl or greater should have a repeat measurement in 1-8 weeks. If the level is within 30 mg/dl (0.8 mmol/L) of the first result, the average of the two values can be used to guide subsequent decisions; otherwise, a third test should be obtained within another 1-8 weeks and the average of the three values used. Getting more than one cholesterol measurement at the outset of treatment is extremely important to assess the patient's serum cholesterol status accurately, because cholesterol levels can fluctuate considerably from day to day in a given individual.[§§]

Most patients with *borderline-high blood cholesterol* levels (200-239 mg/dl) confirmed by two or more readings are given dietary education designed to lower their serum cholesterol level and are followed up annually. However, those individuals in the 200-239 mg/dl range who have definite CHD or two other CHD risk factors (as defined in Table 2) should have lipoprotein analysis and their LDL-cholesterol level determined.

All patients with *high blood cholesterol* levels (240 mg/dl or greater), as well as those with levels 200-239 mg/dl who have definite CHD or two other CHD risk factors (see Table 2), should be tested for the serum level of LDL-cholesterol.

b. Subsequent classification based on **LDL-Cholesterol** *level.*

The action scheme based on LDL-cholesterol level is shown in Figure 4. Two measurements of LDL-cholesterol after an overnight fast are made 1-8 weeks apart, and the average is used for clinical decisions unless the two values differ by more than 30 mg/dl (in which case a third test is carried out, and the average of all three is used). The repeated testing of LDL-cholesterol is important for the same reasons given earlier for total cholesterol—the variability of the level from day to day, and the importance of establishing an accurate baseline upon which to design the best treatment program. It is possible, however, to save time and effort by making the first LDL-cholesterol measurement on the same specimen that is used for the second test of total cholesterol; this is an especially attractive option for patients with very high levels of total cholesterol [above 260 mg/dl (6.7 mmol/L)] on the first test.

LDL-cholesterol levels are classified on the basis of average values as *desirable* [below 130 mg/dl (3.4 mmol/L)], *borderline-high risk* [130-159 mg/dl (3.4-4.1 mmol/L)], or *high risk* [160 mg/dl (4.1 mmol/L) or greater]. Patients with desirable LDL-cholesterol fall into the same class as those with desirable total cholesterol levels (<200 mg/dl), and are given general educational materials and tested again within 5 years. Those with borderline-high-risk LDL-cholesterol (130-159 mg/dl) are given information about and advised to follow a fat-modified diet; they are reevaluated annually unless they have definite CHD or two other risk factors (one of which can be male sex, see Table 2). Such patients (with borderline-high-risk LDL-cholesterol who do have CHD or two other risk factors), together with all patients in the high-risk LDL-cholesterol group (≥160 mg/dl), are clinically evaluated as described below, and then enter a cholesterol-lowering treatment program.

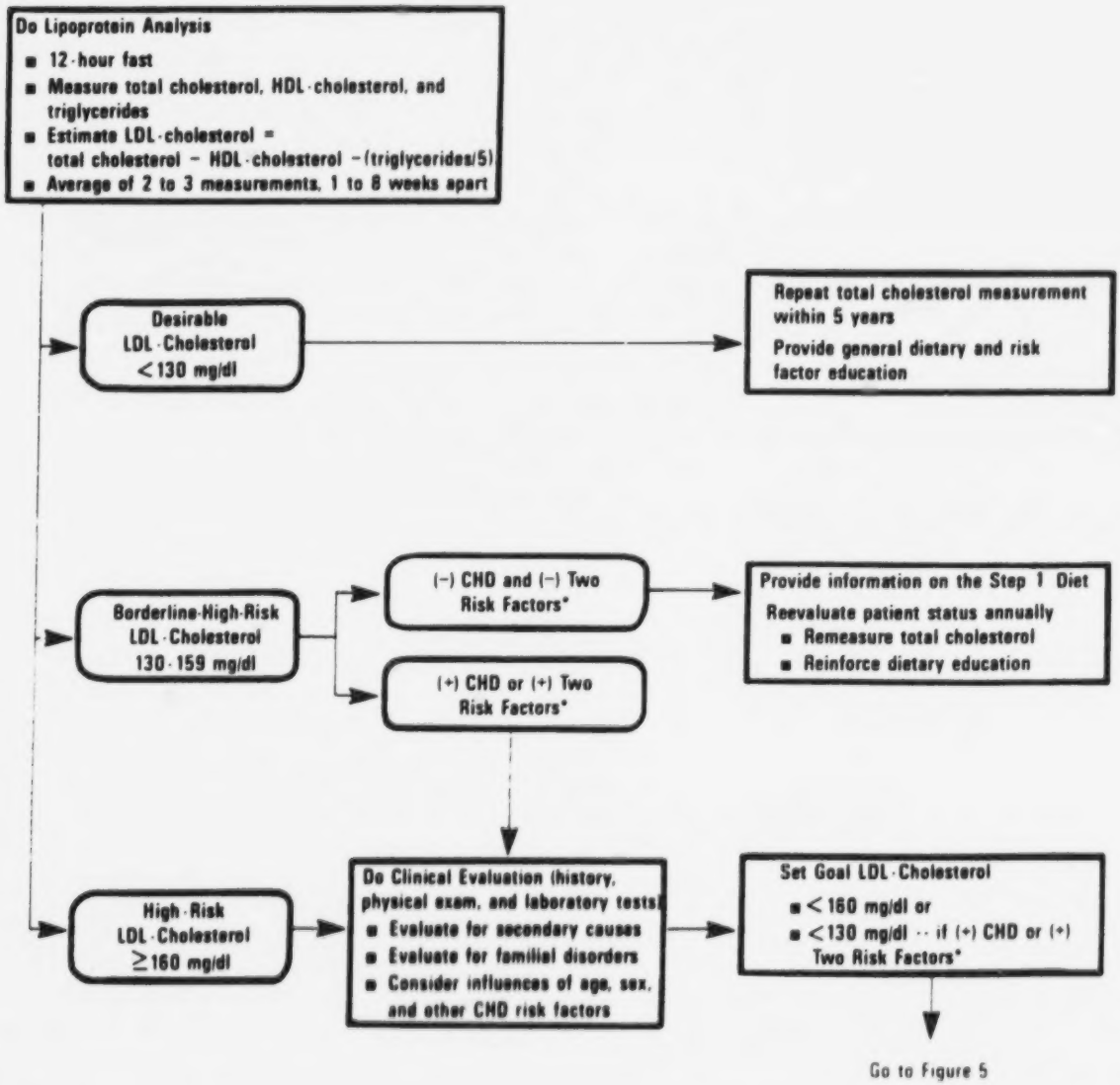
[§§] The standard deviation of repeated measurements in an individual over time has been reported as 18 mg/dl (0.5 mmol/L) for total cholesterol (16) and 15 mg/dl (0.4 mmol/L) for LDL-cholesterol (17).

ERRATA

Page 22. Please substitute the following figure for Figure 4:

FIGURE

4 — *Classification Based on LDL-Cholesterol*


Do Lipoprotein Analysis
■ 12-hour fast
■ Measure total cholesterol, HDL-cholesterol, and triglycerides
■ Estimate LDL-cholesterol = total cholesterol − HDL-cholesterol − (triglycerides/5)
■ Average of 2 to 3 measurements, 1 to 8 weeks apart
Desirable LDL-Cholesterol <130 mg/dl
Repeat total cholesterol measurement within 5 years
Provide general dietary and risk factor education
Borderline-High-Risk LDL-Cholesterol 130-159 mg/dl
(−) CHD and (−) Two Risk Factors*
(+) CHD or (+) Two Risk Factors*
Provide information on the Step 1 Diet
Reevaluate patient status annually
■ Remeasure total cholesterol
■ Reinforce dietary education
High-Risk LDL-Cholesterol ≥160 mg/dl
Do Clinical Evaluation (history, physical exam, and laboratory tests)
■ Evaluate for secondary causes
■ Evaluate for familial disorders
■ Consider influences of age, sex, and other CHD risk factors
Set Goal LDL-Cholesterol
■ <160 mg/dl or
■ <130 mg/dl -- if (+) CHD or (+) Two Risk Factors*
Go to Figure 5

*One of which can be male sex (see Table 2).

3. *Methods of Detection.*

Serum *total cholesterol* levels can be measured at any time of day in the nonfasting state, since total cholesterol concentrations do not change appreciably after a fat-containing meal. Patients should be following their ordinary eating habits and in their usual state of health. Patients who are acutely ill, are losing weight, are pregnant, or have had a myocardial infarction within the past 3 months should be rescheduled; the cholesterol levels obtained in such patients may not be representative of their usual levels. To prevent an effect of posture or stasis on the cholesterol determination, venipuncture should be carried out on patients who have been in the sitting position for at least 5 minutes, and the tourniquet should be used for as brief a period as possible. The blood may be collected either as serum (no anticoagulant) or as plasma (in EDTA). If blood is obtained without anti-coagulant, it should be allowed to clot for 30 minutes at room temperature, and the clot should be detached from the wall of the tube prior to centrifuging. Rapid capillary blood (fingerstick) methodology for cholesterol measurement is currently under development and evaluation. Should this methodology prove reliable, it could be suitable for initial cholesterol determinations.

LDL-cholesterol determinations can also be carried out on either serum or plasma, provided that, as with total cholesterol measurements, plasma values are multiplied

TABLE 2. — *Risk status based on presence of CHD risk factors other than LDL-cholesterol*

The patient is considered to have a high risk status if he or she has one of the following:
EITHER:
Definite CHD: the characteristic clinical picture and objective laboratory findings of either:
■ Definite prior myocardial infarction, or
■ Definite myocardial ischemia, such as angina pectoris
OR:
Two other CHD risk factors:
■ Male sex*
■ Family history of premature CHD (definite myocardial infarction or sudden death before age 55 in a parent or sibling)
■ Cigarette smoking (currently smokes more than 10 cigarettes per day)
■ Hypertension
■ Low HDL-cholesterol concentration (below 35 mg/dl confirmed by repeat measurement)
■ Diabetes mellitus
■ History of definite cerebrovascular or occlusive peripheral vascular disease
■ Severe obesity (≥30% overweight)

* Male sex is considered a risk factor in this scheme because the rates of CHD are 3-4 times higher in men than in women in the middle decades of life and roughly 2 times higher in the elderly. Hence, a man with one other CHD risk factor is considered to have a high risk status, whereas a woman is not so considered unless she has two other CHD risk factors.

by 1.03 to correct them to the serum cutpoints specified in this report. However, because the LDL-cholesterol value is estimated from measurements of other lipids including triglyceride, blood samples should be collected from patients who have fasted for at least 12 hours (except for water or black coffee).

LDL-cholesterol level is estimated from measurements of the levels of total cholesterol, total triglycerides, and HDL-cholesterol. If the triglyceride value is below 400 mg/dl (4.5 mmol/L), then this value can be divided by five to estimate the VLDL-cholesterol level. Since total cholesterol is the sum of LDL-cholesterol, HDL-cholesterol, and VLDL-cholesterol, LDL-cholesterol can be calculated as follows (all quantities are in mg/dl):

LDL-cholesterol = total cholesterol – HDL-cholesterol – (triglyceride/5) (18)[##]

If the triglyceride value is above 400 mg/dl, LDL-cholesterol estimation by the above formula becomes less accurate. For such patients, ultracentrifugation in a specialized laboratory can be used to give a more accurate LDL-cholesterol level; it may be appropriate to refer such patients to a lipid specialist.

The choice of laboratory is an important issue because there is considerable variability in the accuracy with which laboratories measure cholesterol. This measurement variability is another reason for recommending that more than one cholesterol measurement be obtained and average values be used at key decision points in this report. All recommendations about cholesterol levels in this report presuppose accurate and reliable measurements. The physician should seek a laboratory that participates in a suitable standardization program. The issue of laboratory methods and their standardization is being addressed by the Laboratory Standardization Panel of the National Cholesterol Education Program.

4. *Clinical Evaluation.*

All patients with an LDL-cholesterol level ≥160 mg/dl, and those with a level of 130-159 mg/dl and high risk status as defined above in Table 2, should be evaluated clinically. They should then be assigned a goal LDL-cholesterol level and enter the program for cholesterol-lowering treatment.

The clinical evaluation, which includes a history, physical examination, and basic laboratory tests, has three aims. The first is to determine whether the high LDL-cholesterol level is caused by another disease or by a drug. The second is to determine whether a genetic disorder may underlie the elevated LDL-cholesterol. The third aim is to ensure that the patient is fully characterized with regard to age, sex, and the presence or absence of definite CHD and of other CHD risk factors, in order to use this information in decisions about treatment directed at LDL-cholesterol.

a. Secondary high blood cholesterol.

The clinical evaluation for secondary (and possibly reversible) forms of high-risk

[##]A recent report suggests that, in this formula, dividing the triglyceride value by 6, rather than 5, may provide a more accurate estimation of the LDL-cholesterol level (19). Further studies may validate the use of triglyceride/6 as the preferred way of estimating LDL-cholesterol.

LDL-cholesterol includes consideration of, and where appropriate ruling out, the following conditions:

- Hypothyroidism
- Nephrotic syndrome
- Diabetes mellitus
- Obstructive liver disease
- Drugs that may raise LDL-cholesterol levels, particularly progestins and anabolic steroids.

High blood cholesterol secondary to other diseases or drugs can be detected by clinical evaluation and, when indicated, by the following laboratory tests: urinalysis, complete blood count, and serum TSH, glucose, alkaline phosphatase, and albumin. When one of the causes of secondary high cholesterol is present, the usual approach is to treat the disease or discontinue the drug (if possible) and then to reevaluate the LDL-cholesterol level.

b. Familial disorders.

In most cases, high blood cholesterol is not secondary to some other condition, and the patient has a primary form of LDL-cholesterol elevation. This can be either genetic (familial) or sporadic (often diet induced), and the next step is to consider which of these possibilities is more likely. Diagnosing genetic disorders helps clarify the etiology and management of LDL-cholesterol elevations in affected patients, and emphasizes the desirability of measuring cholesterol in first-degree relatives (parents, siblings, children) in order to identify those who may need cholesterol-lowering treatment.

The genetic hyperlipidemias are described in Appendix II; two important ones are summarized here. One of these is familial hypercholesterolemia (FH), an autosomal dominant disorder of the LDL receptor. Heterozygotes with this disorder have a population frequency of about 1 in 500 and often have serum cholesterol levels greater than 300 mg/dl, tendon xanthomas, and premature CHD. Another important genetic cause of high-risk LDL-cholesterol levels is familial combined hyperlipidemia (FCHL). Affected family members may have high serum levels of LDL-cholesterol, or of triglyceride, or both. Such patients generally do not have tendon xanthomas, but premature CHD is common. The prevalence of these two familial disorders among survivors of myocardial infarction under 60 years of age is 5% for FH and 15% for FCHL (20).

c. Other lipid risk factors.

The level of plasma HDL-cholesterol is inversely related to CHD rates in most epidemiologic studies even after adjustment for the influence of other risk factors (see Appendix II). Although there is no direct experimental evidence that raising HDL-cholesterol levels reduces the risk of CHD, the lifestyle interventions that raise the level of this lipoprotein—quitting smoking, reducing obesity, and exercising—are good advice for other reasons and should be recommended to all patients regardless

of their HDL-cholesterol levels. One other lifestyle approach to increasing the level of HDL-cholesterol—increasing the intake of alcohol—is not recommended because of the possibility of encouraging excessive intake. The issue of low HDL-cholesterol and its management is discussed further in Appendix II.

Reliance on a ratio of either total or LDL-cholesterol to HDL-cholesterol as a key factor in decisions regarding treatment is not a practice recommended in this report. Blood pressure and smoking are not combined into a single number because the clinician needs to know both facts separately in order to recommend an intervention. Similarly, HDL-cholesterol and LDL-cholesterol are independent risk factors with different determinants, and combining them into a single number conceals information that may be useful to the clinician. HDL-cholesterol does, however, contribute to decisions about treatment for LDL-cholesterol, because a low level increases the CHD risk of the patient (see Table 2).

The level of plasma triglyceride is also a risk factor for CHD in most epidemiologic studies. In general, however, it is not an independent risk factor, i.e., the association usually disappears when statistically adjusted for plasma total cholesterol and HDL-cholesterol levels. In the Framingham Study, however, the plasma triglyceride level was found to be an independent predictor of CHD risk in women (21). The recommended approach to the problem of hypertriglyceridemia is described in the report of the NIH Consensus Development Conference on Treatment of Hypertriglyceridemia (22) and is summarized in Appendix II. In the absence of pathophysiologic or animal evidence that triglyceride is atherogenic or that lowering the plasma level lowers the risk of CHD, intervention specifically directed at this lipid (except in the rare patient with a very high level that may cause pancreatitis) is not generally recommended at this time. On the other hand, many individuals with elevated triglycerides have associated low levels of HDL-cholesterol and/or high levels of LDL-cholesterol, which do influence decisions about intervention to reduce the risk of CHD in ways described in this report. Moreover, hypertriglyceridemia alone may be a marker for familial combined hyperlipidemia, which warrants therapy to prevent CHD.

d. Other major (nonlipid) risk factors.

Information on whether CHD or its other risk factors are present is used to assess whether the patient has reasons unrelated to LDL-cholesterol for being at high risk of a CHD event or death. The search is important because modifiable risk factors such as hypertension and cigarette smoking are themselves important targets for intervention. In addition, the presence of any risk factor, whether modifiable or not, influences clinical decisions about LDL-cholesterol because the increased absolute level of risk may increase the potential benefit from lowering the level of LDL-cholesterol (see Table 1).

This principle can be used in a general way by the clinician, and also as a specific rule in the decision schemes set out in Figures 3 and 4. In Figure 4 the presence of high risk status due to factors other than LDL-cholesterol establishes a lower

cutpoint for triggering intervention and a lower therapeutic goal for LDL-cholesterol. The definitions of high risk status are given in Table 2. Because the presence of CHD is by far the strongest factor that influences the risk of recurrent CHD events or death, it is particularly important in clinical decisions for treating LDL-cholesterol. Thus, this report emphasizes the importance of both primary and secondary prevention.

e. Race, sex, and age.

The percentage of adults with high blood cholesterol by age, race, and sex is given in Table 3. The prevalence rises with age to plateau at about 50 years of age, and does not vary appreciably by race or sex except for the higher prevalence in older women. (This high prevalence in older women is due to the fact that they have high levels of both LDL- and HDL-cholesterol.) Additional information on the distributions of total and LDL-cholesterol levels in the population is given in Appendix I. This section addresses the CHD risk in different groups, with the implications for managing LDL-cholesterol.

■ *Race:*

Race is not included in Table 2 because available evidence suggests that the clinical management of LDL-cholesterol should not differ according to race in the United States. (This report is not specifically directed at populations in other countries, but the guidelines would probably apply reasonably well to any country where CHD is endemic at similar levels to those in the United States.)

■ *Sex:*

Sex, on the other hand, should be considered as a risk factor, as described in Table 2, when determining the risk status of an individual patient. In women as in men, CHD is the major cause of death, and cholesterol levels are predictive of CHD. However, the rates of CHD are 3-4 times higher in men than in women in the middle decades of life and roughly 2 times higher in the elderly (24,25). Hence, the absolute magnitude of the potential benefit from lowering blood cholesterol in general, and the benefit/risk ratio of drug therapy in particular, is greater for men

TABLE 3. — *U.S. Prevalence of High Blood Cholesterol (serum concentration ≥ 240 mg/dl) by Age, Race, and Sex (% of each population)* (23)

than for women. Thus, male sex is considered a risk factor in decisions about the cutpoints and goals of cholesterol-lowering treatment.

■ *Age:*

Age is a complicated factor to consider. Beginning at 20 years of age the mean total and LDL-cholesterol levels increase by about 40 mg/dl (1.0 mmol/L) during the next 2 to 3 decades; in the elderly, the levels decline slightly (see Appendix I for age-specific tables). Two major LDL-cholesterol cutpoints are recommended in this report: 160 mg/dl identifies the group with high-risk LDL-cholesterol, and (as discussed later in the section on drug treatment) 190 mg/dl (4.4 mmol/L) identifies the group with "very high-risk" LDL-cholesterol for whom consideration of drug therapy is warranted even in the absence of other risk factors. These cutpoints approximate the 75th and 90th percentiles for 35-60 year-old patients. Using these same cutpoints in younger patients will have the effect of designating a smaller proportion of the younger population as being in the high-risk categories.

The strategy recommended by the Cholesterol Consensus Development Conference for making clinical decisions about patients 20-39 years of age is to use cutpoints that correspond to the age-specific 75th and 90th percentile values (see Appendix I). Using the Consensus Conference recommendations concerning the 75th percentile values, adults 20-29 years of age would be considered (in the terminology of the present report) to have high blood cholesterol for levels exceeding 200 mg/dl; those 30-39 years of age would be in this category if total cholesterol exceeded 220 mg/dl (5.7 mmol/L). Giving dietary treatment to the top 25% of the young adult population is probably desirable in order to prevent the development of atherosclerosis at an earlier stage in the disease. Recommending drug treatment to as large a group as the top 10% of young adults, however, is premature until additional evidence becomes available on the safety of using lipid-lowering drugs for many decades. There is, moreover, the important fact that age is a very strong risk factor, and therefore the absolute magnitude of the benefit (and the benefit/risk ratio) increases with age for the reasons given earlier.

Patients 60 years of age and above are another issue. There is little direct clinical trial evidence on whether elderly patients will benefit from intervention, and the strength of the association between LDL-cholesterol and CHD diminishes with age. However, LDL-cholesterol does continue to have some association with CHD, and the clinical trial evidence for the effectiveness of intervention after myocardial infarction suggests that lowering LDL-cholesterol is beneficial even in patients who already have advanced disease. Moreover, the fact that age is associated with a high risk of CHD in the later decades of life means that the absolute magnitude of the potential benefits of intervention remains substantial in the elderly (25).

Summarizing the issue of sex and age, the recommendations and cutpoints in this report are meant to apply to all adults 20 years of age and above. There is room, however, for modifications based on the judgment of the physician and the preferences of the patient when dealing with individual patients, particularly young adults, the elderly, and women.

A. Cutpoints and Goals for Dietary Therapy

Patients with high-risk LDL-cholesterol levels (≥160 mg/dl), and those with borderline-high-risk LDL-cholesterol (130-159 mg/dl) who also have definite CHD or two other risk factors (see Table 2), should enter a program of dietary therapy instituted by the physician. The *minimal* goals of therapy are: (1) to lower LDL-cholesterol to below 160 mg/dl if the patient has neither definite CHD nor two other CHD risk factors (see Table 2); or (2) to lower LDL-cholesterol to below 130 mg/dl if definite CHD or two other CHD risk factors (see Table 2) are present. Ideally, dietary means should be used to attain even lower levels of LDL-cholesterol, if possible, to achieve a further reduction in CHD risk.

Although the goal of therapy is to lower the LDL-cholesterol concentration, measurement of serum total cholesterol can be used to monitor the response to diet. The principle is that LDL-cholesterol should be used for the definitive classification of patients and for decision making, but total cholesterol can be substituted for monitoring. For simplicity, a serum total cholesterol of 240 mg/dl corresponds roughly to an LDL-cholesterol of 160 mg/dl, while a total cholesterol of 200 mg/dl corresponds roughly to an LDL-cholesterol of 130 mg/dl. Thus, as a guide for monitoring, the minimal goals of therapy are: (1) to lower total cholesterol to below 240 mg/dl, if the patient has neither definite CHD nor two other CHD risk factors, or (2) to lower total cholesterol to below 200 mg/dl if definite CHD or two other risk factors are present. It should be emphasized again that even lower levels of total cholesterol are desirable. The use of total cholesterol as a surrogate for LDL-cholesterol applies to patients with average levels of HDL-cholesterol without high total triglyceride levels. If the patient is found to have an abnormally high or low HDL-cholesterol or hypertriglyceridemia upon initial classification, so that total cholesterol is not a good surrogate for LDL-cholesterol, it is appropriate to use LDL-cholesterol even in monitoring. After the cholesterol response to diet has been obtained, LDL-cholesterol should again be measured in order to decide whether or not the goal of therapy has been achieved. In addition, levels of LDL-cholesterol should be employed for making a decision about drug therapy.

B. Overview and General Approach

Three dietary habits typically contribute significantly to elevated plasma cholesterol. First is a high intake of saturated fatty acids. The average intake is 13-15% of total calories, but many Americans consume 15-20% of their calories as saturated fatty acids. Second is a relatively high intake of cholesterol. Many patients with high-risk LDL-cholesterol levels exceed the current average intake of about 350-450 mg per day. Third is a high caloric intake that exceeds body requirements commonly

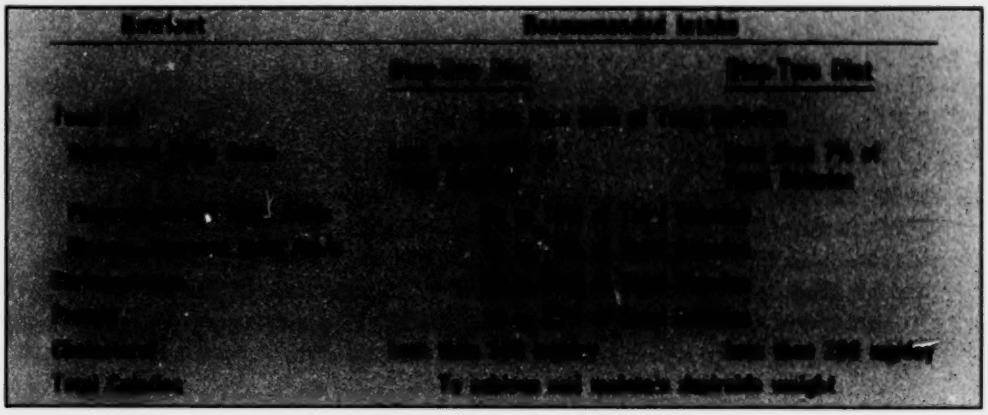
causing obesity. The aim of dietary therapy is to reverse these excesses while maintaining and promoting good nutrition.

This document is directed at the high-risk patient, and its underlying theme is specific therapy for high blood cholesterol. Modification of the diet is an essential element in this therapy. The initial diet modifications recommended for patients in this report are very similar to the diet modifications recommended by the American Heart Association and other organizations for the public at large, as part of a population-based approach for lowering cholesterol. In the program described in this report, however, diet recommendations are provided to patients, in a medical treatment setting, in an intensive manner. Accordingly, the dietary intervention described here is referred to as "dietary treatment." It should be noted that the diets recommended in this report are consistent with good nutrition, and that their aim is to achieve healthy eating patterns. Physicians should emphasize to patients that the goal is not a temporary "diet," but a permanent change in eating behavior.

Diet modification should occur in two steps, which are outlined and compared in Table 4. These diets are designed to progressively reduce the intake of saturated fatty acids and cholesterol and eliminate excess total calories. The Step-One Diet should be prescribed by the physician and implemented by the physician and his or her immediate staff. This diet calls for an intake of total fat less than 30% of calories, saturated fatty acids less than 10% of calories, and cholesterol less than 300 mg/day. The patient's serum cholesterol level should be measured at 4-6 weeks and at 3 months after starting the Step-One Diet.

If the minimal goals of therapy are not achieved on this diet by 3 months, the patient should usually progress to the Step-Two Diet. Adoption of the Step-Two Diet would be facilitated by referral to a registered dietitian. This diet calls for a further reduction in saturated fatty acid intake to less than 7% of calories and cholesterol intake to less than 200 mg/day.

TABLE 4. — *Dietary Therapy of High Blood Cholesterol*



For many high-risk patients, the goals of cholesterol lowering can be achieved by dietary therapy alone. It is important that dietary therapy not be regarded as a failure prematurely. For most patients, dietary therapy should be continued for at least 6 months before adding drug therapy. Exceptions include patients with very high LDL-cholesterol levels and other severe dyslipidemias (see Appendix II). If the desired goals of LDL-cholesterol lowering are met by diet modification alone, long-term monitoring is indicated. If reduction of LDL-cholesterol is not satisfactory, lipid-lowering drugs should be considered along with continued dietary intervention.

C. *Recommended Diets*

1. *Step-One and Step-Two Diets—Nutrients and Rationale.*

The recommended diets are presented in two steps—the Step-One and Step-Two Diets. The Step-One Diet calls for the reduction of the major and obvious sources of saturated fatty acids and cholesterol in the diet; for many patients this can be achieved without a radical alteration in dietary habits. The Step-Two Diet requires careful attention to the whole diet so as to reduce the intake of saturated fatty acids and cholesterol to a minimal level compatible with an acceptable and nutritious diet. Saturated fatty acids and cholesterol are not essential nutrients, and neither is required in the diet. The body can make these lipids in abundance, and they can be transported from one tissue to another to assure that any local shortage is supplied by lipids produced elsewhere in the body. The real need then is to reduce dietary saturated fatty acids and cholesterol to the levels required to achieve the goals of LDL-cholesterol lowering and still provide a diet that is nutritious and palatable. The fat-modified diets proposed in this report are designed to achieve these aims. The rationale for the recommended characteristics of the Step-One and Step-Two Diets can be described briefly.

a. A nutritionally balanced diet.

A prerequisite for any therapeutic diet is that it be nutritionally adequate (26). It must contain sufficient amounts of vitamins, minerals, and macronutrients to meet recommended allowances. The diet should contain a variety of foods. Fruits, vegetables, and legumes (peas and beans) are good sources of vitamin A, vitamin C, folic acid, fiber, and many minerals. Whole-grain and enriched breads, cereals, and other grain products contain B vitamins, protein, fiber, and some iron. Poultry and fish are good sources of protein. Meat products are rich in protein and contain iron in a form that is well absorbed; thus, meat can be included in a diet otherwise designed to lower serum cholesterol, although meat fat needs to be curtailed. The same is true of milk products; the nonfat portion of milk is rich in calcium and contains protein. While egg yolks are rich in cholesterol, egg whites contain protein and no cholesterol. Most nuts contain protein and fat, but their fat is largely

unsaturated and thus does not raise the serum cholesterol level. Thus, while a serum cholesterol-lowering diet requires modification of fat, the diet should be nutritious and palatable and include a variety of foods. The following considers the specific modifications that will be required.

b. Total fat.

Total fat intake in both therapeutic diets should not exceed 30% of total calories. The purpose of decreasing total fat intake is twofold—to facilitate reduction of saturated fatty acid intake and to promote weight reduction in overweight patients by substituting foods of lower caloric density. Total fat in the current American diet averages approximately 35-40% of calories. Hence for most high-risk patients, about one-fifth of their total fat now consumed must be eliminated. In the past, one approach to more intensive dietary therapy of high blood cholesterol (beyond the Step-One Diet) has been to reduce intake of total fat to 20% or less of calories, in parallel with progressive reductions in saturated fatty acids and cholesterol. However, very low fat intakes have low satiety value and often are not well accepted. Recent evidence indicates that a marked reduction in dietary fat is not required for satisfactory lowering of plasma LDL, provided that saturated fatty acids are reduced and the remaining fat is mainly unsaturated. In other words, a decrease in total fat to below 30% of calories may not be needed for the sole purpose of lowering the plasma cholesterol level. Nevertheless, a reduction in total fat to near 20% of calories will facilitate weight reduction and a decrease in saturated fatty acid intake for some patients. For these reasons, a further reduction of fat intake is not required in the Step-Two Diet, but neither is it excluded.

c. Saturated fatty acids.

In the Step-One Diet, saturated fatty acids should be decreased to less than 10% of calories. For most patients, saturated fatty acid intake will have to be reduced by about one-third to meet the requirements of the Step-One Diet, and another third for the Step-Two Diet. Several dietary fats are rich in saturated fatty acids. Animal fats that are high in saturated fatty acids include butter fat—contained in butter itself, whole milk, cream, ice cream, and cheese—beef fat, and pork fat. In addition, three plant oils—palm oil, palm kernel oil, and coconut oil—are especially rich in saturated fatty acids.

d. Polyunsaturated fatty acids.

When dietary saturated fatty acids are decreased, they can be replaced in part by polyunsaturated fatty acids. The polyunsaturates can be increased to 10% of calories, but they should not exceed this value. The current American diet contains about 7% of calories as polyunsaturated fatty acids, which should be a minimum value for the therapeutic diets. There are two major categories of polyunsaturated fatty acids, commonly referred to as omega-6 and omega-3. The major omega-6 fatty acid is linoleic acid, which has 18 carbon atoms and two double bonds. Substitution of linoleic acid for dietary saturated fatty acids results in a fall in plasma cholesterol. Although very high intakes of linoleic acid were once advocated for cholesterol lowering, lack of information about the consequences of long-term

ingestion of large amounts of linoleic acid has led most investigators to recommend a ceiling of 10% of total calories. Several vegetable oils are rich in linoleic acid, including safflower oil, sunflower seed oil, soybean oil, and corn oil. Although polyunsaturated oils are high in linoleic acid and low in saturated fatty acids, they also are high in total calories (as are all fats and oils); consequently they can promote weight gain if consumed in large amounts.

The major sources of omega-3 fatty acids are the fish oils. Most omega-3 fatty acids in fish oil have very elongated carbon chains and are highly polyunsaturated. The major acids in this class are eicosapentaenoic acid (EPA) and docosahexaenoic acid (DHA). The omega-3 fatty acids have been found to lower triglyceride levels when given in high doses, but they are not necessarily the desired therapy for hypertriglyceridemia (see Appendix II). There is little evidence that omega-3 fatty acids are useful for reducing LDL-cholesterol levels. Although it has been postulated by some that they will reduce the risk for CHD, this has not been established. Furthermore, it is not known whether long-term ingestion of these fatty acids will lead to undesirable side effects. The use of fish-oil capsules as a supplement in a therapeutic diet for high-risk cholesterol levels is not recommended here.

Consumption of omega-3 fatty acids should be differentiated from that of fish. Some fish are rich in omega-3 acids while others are not. Epidemiological data suggest that frequent consumption of fish of any type, seemingly independent of omega-3 fatty acids, is associated with reduced CHD risk. Whether this is true or not, fish can serve as a useful substitute for meats that are richer in saturated fatty acids.

e. Monounsaturated fatty acids.

In both therapeutic diets, monounsaturated fatty acids, mainly oleic acid, should comprise 10-15% of total calories. Oleic acid is the major fatty acid found in olive oil, rapeseed (canola oil), and high-oleic forms of sunflower seed oil and safflower oil. For many years, oleic acid was considered to be "neutral" in its effect on plasma cholesterol, neither raising nor lowering the cholesterol level. However, recent evidence indicates that oleic acid may cause as much of a decrease in LDL-cholesterol levels as linoleic acid when either is substituted for saturated fatty acids in the diet. The current American diet contains 14-16% of calories as monounsaturated fatty acid. Much of it is consumed with animal fats, which are rich in saturated fatty acids. When animal fats are curtailed, a larger portion of monounsaturated fatty acids can come from vegetable oils.

f. Dietary cholesterol.

Dietary cholesterol causes marked hypercholesterolemia and atherosclerosis in many laboratory animals, including nonhuman primates. Although high intakes of cholesterol in humans rarely cause striking rises in the plasma cholesterol level, controlled metabolic studies show that dietary cholesterol usually raises the plasma cholesterol level. The degree of rise varies from person to person. Overall, excess dietary cholesterol appears to contribute to the high LDL-cholesterol levels seen in

high-risk patients and thus may add to CHD risk. Furthermore, concern about dietary cholesterol extends beyond its effects in raising the LDL-cholesterol level. Newly absorbed cholesterol enters the circulation with chylomicrons, which are degraded to cholesterol-rich chylomicron remnants; the latter may be atherogenic. Dietary cholesterol is not required for normal body function.

For practical purposes a cholesterol intake of less than 300 mg/day is reasonable as part of the first step in dietary management of high-risk LDL-cholesterol. However, further restriction, as recommended in the Step-Two Diet, is justified for patients who do not achieve the goals of therapy on the Step-One Diet despite adherence. Cholesterol in the diet comes from animal products. Particularly rich sources are egg yolk and organ meats (liver, sweetbreads, and brain). Some shellfish (e.g., shrimp) also are moderately high in cholesterol, but not to the extent of egg yolk or organ meats. The flesh of all animals (beef, pork, lamb, chicken, fish) contains cholesterol; it is present in both muscle and fat, and both have approximately the same concentrations on a wet-weight basis. Dairy products containing butter fat also contribute cholesterol to the diet.

g. Protein.

The recommended intake of protein in both therapeutic diets is between 10% and 20% of calories. In laboratory animals, certain plant proteins have a cholesterol-lowering action relative to animal proteins. The same effect has not been established in humans. Thus, the type of protein in the therapeutic diets is not specified.

h. Carbohydrate.

Both recommended diets specify an intake of carbohydrates of 50% to 60% of calories. When dietary fat is reduced, it should be replaced by carbohydrate. Dietary carbohydrates include simple sugars (monosaccharides and disaccharides), complex digestible carbohydrates (starches), and complex indigestible carbohydrates (fiber). Complex carbohydrate should comprise more than half of digestible carbohydrates; this will help ensure ingestion of desirable quantities of vegetable products that contain vitamins, minerals, and fiber. In most people, when digestible carbohydrates are substituted for cholesterol-raising saturated fatty acids, the LDL-cholesterol level will fall to about the same extent as when oleic acid and linoleic acid are substituted in this manner. Very high-carbohydrate diets can raise plasma triglycerides, but when fat intakes are in the vicinity of 30% of calories, this triglyceride response is minimal.

i. Total calories.

Obesity is not only associated with elevated serum LDL-cholesterol levels but is an independent risk factor for CHD. An important recommendation therefore is to reduce caloric intake to achieve weight reduction in overweight patients. Weight reduction will lower the LDL-cholesterol level in many people, as well as reduce plasma triglycerides and raise HDL-cholesterol levels. Some patients with high-risk LDL-cholesterol levels are extremely sensitive to caloric intake, and weight

reduction and establishment of desirable body weight will completely correct their elevated LDL-cholesterol concentrations. The importance of caloric restriction in overweight, high-risk individuals cannot be overemphasized.

Weight reduction can be facilitated by exercise. Experience has shown that regular exercise will curb the appetite as well as burn off excess calories. It also will lower serum triglycerides and raise HDL-cholesterol levels, and in some individuals, may lower the LDL-cholesterol level.

j. Fiber.

The indigestible carbohydrates and related polymers come under the category of dietary fiber. One type of fiber is insoluble, an example of which is the cellulose found in wheat bran. Insoluble fiber adds bulk to the stools and contributes to normal colon function. Some authorities believe that relatively high intake of dietary fiber may help prevent diverticulosis and colon cancer, although this remains to be proven. Excessive intakes of insoluble fibers can be associated with gastrointestinal side effects and even interfere with absorption of vital nutrients such as calcium. Dietary fibers such as cellulose appear to have very little or no effect on blood cholesterol levels.

Another type of fiber is soluble in the intestine but not absorbed. This category includes pectins, certain gums, and psyllium. One of the gums is beta-glucan, which is present in oat products and beans. High intakes (e.g., 15 to 25 g/day) of soluble fiber have been reported to lower the plasma cholesterol level by 5 to 15%. These high intakes can produce gastrointestinal side effects, but prolonged usage frequently is associated with improved tolerance.

k. Alcohol.

The average intake of alcohol among Americans is approximately 5% of total calories, but this value varies widely among individuals. Although alcohol is not harmful when taken in moderation, a high consumption is known to have many adverse effects on health. Alcohol affects lipoprotein metabolism in several ways. It does not affect LDL-cholesterol concentrations, but it does increase triglyceride concentrations and HDL-cholesterol levels in many individuals. The mechanism for the rise in HDL-cholesterol is not known, nor is it known whether the higher level so produced imparts any protection against CHD. For patients who can consume moderate amounts of alcohol responsibly, its use can be allowed in the context of the above reservation. However, this report does not specifically recommend use of alcohol in the prevention of CHD.

2. *Expected Responses to Dietary Therapy.*

The degree of reduction of LDL-cholesterol levels that can be achieved by dietary therapy depends on the dietary habits of the patient before starting the diet and on the inherent responsiveness of the patient. In general, patients with high cholesterol levels show a greater absolute reduction in total and LDL-cholesterol concentrations

than do individuals with relatively low cholesterol levels. Metabolic ward studies suggest that switching from the typical American diet to the Step-One Diet could reduce cholesterol levels on average by 30-40 mg/dl. Advancing to the Step-Two Diet can be expected to cause a further decline of approximately 15 mg/dl in cholesterol levels. Some individuals may demonstrate even greater reductions on the two diets, and others will have lesser responses. Most of the decrease in total blood cholesterol occurs in the LDL fraction.

D. Practical Approach to Dietary Therapy

1. *Outline of Approach.*

Once a patient is deemed at high risk, dietary therapy should begin in the physician's office. Diet is the cornerstone of treatment of high-risk cholesterol levels. The view that diet modification is impractical or doomed to failure for most patients is not justified. Many individuals have successfully modified their diets and have obtained a substantial reduction in cholesterol levels. Much of the problem of high cholesterol levels among Americans is due to dietary excesses, and diet modification is the rational approach to this problem for most people.

a. Role of the physician.

The success of dietary therapy will depend to a large extent upon the physician's attitudes, knowledge, and skills in motivating the patient and in organizing a team approach to dietary therapy. The physician can have a major impact on the patient's attitude toward diet modification. A positive attitude on the part of the physician is absolutely vital. The physician should describe to the patient his/her category of high blood cholesterol and should give an overview of the therapeutic plan. The role of diet and possibly drugs should be discussed. The physician will need to review the patient's past dietary history. The patient should be questioned about current dietary habits with special attention to intake of foods rich in saturated fatty acids and cholesterol (e.g., dairy fats—milk, butter, cheese, ice cream—frequency and choices of meat products, bakery goods, eggs, and organ meats). The need to modify eating behavior to achieve the goals of therapy should be indicated, and the plan for carrying out dietary treatment, as it involves other members of the team, can be described. Finally, the physician has a vital role to play in the monitoring of response, in reinforcement of the diet message, and in leadership of the therapeutic team. For assessing adherence to the diet, the physician can review the contents of Table 5 with the patient at follow-up visits.

b. Role of the physician's staff.

Another key component of the therapeutic team is the physician's staff. This may include registered nurses, registered physician's assistants, nurse clinicians, and

other types of assistants. These individuals should receive appropriate training for their roles in patient management, which will include aiding in further dietary assessment and in dietary education and counseling. Nurses and other assistants can play key roles in patient education (e.g., rationale for dietary change, selection of appropriate foods), in promoting behavioral changes, and in monitoring dietary changes. Various educational materials produced by the National Cholesterol Education Program and the American Heart Association can be used to assist in dietary education for patients. Referral to a registered dietitian can facilitate dietary instruction and monitoring of adherence, but if the physician's staff is appropriately trained, it can perform these functions for many patients.

c. Role of registered dietitians.

Registered dietitians (RDs) are educated in the science of nutrition and are professionally trained in dietary intervention. They must meet uniform standards for registration. The term "nutritionist" is used in a variety of ways. Some nutritionists are registered dietitians, but others may not be registered and may not have the clinical training in dietary counseling of a registered dietitian. Although such nutritionists may play a role in dietary education, referral to a registered dietitian is particularly valuable for more intensive dietary therapy, such as the Step-Two Diet, and evaluation of nutritional adequacy. Patients who have had difficulty in adhering or responding to the Step-One Diet also have much to gain from counseling by a registered dietitian. Patients who are not initially successful in the Step-One Diet may be referred to a dietitian for another Step-One Diet trial period before progressing to the Step-Two Diet. For some patients, based on the physician's judgment, referral to a registered dietitian may be appropriate from the outset of dietary therapy.

Dietitians can be identified through a local hospital as well as through State and district affiliates of the American Dietetic Association. The American Dietetic Association (208 South LaSalle Street, Chicago, IL 60604) maintains a roster of dietitians and responds to requests in writing for assistance in locating a registered dietitian in a given area. Dietitians with particular expertise in cholesterol management are available in most large medical centers where they are often part of a multidisciplinary lipid clinic team or cardiac rehabilitation team. The local affiliate of the American Heart Association may have a listing of dietitians who have particular interest and expertise in modifying the diet for purposes of cardiovascular risk reduction.

d. Schedule of dietary therapy.

Adherence to the prescribed diet is facilitated by monitoring the patient's response. The Step-One Diet should be employed for three months, and if the desired response is not obtained in spite of good diet adherence, the patient can progress to the Step-Two Diet for another three months. During this period, serum cholesterol levels should be monitored at regular intervals (described below). For most patients, dietary therapy to lower serum total and LDL-cholesterol should be employed for at least six months before considering drugs. Exceptions to this approach are patients

with severe elevations of blood cholesterol (see Appendix II) and patients with definite CHD.

2. *Recommended Dietary Patterns.*

Most patients should be able to adopt and adhere to the Step-One Diet. Table 5 outlines ways to achieve the goals of dietary therapy, and a copy may be given to the patient along with additional educational materials. It should be emphasized to the patient that the recommended diet can be both tasty and nutritious and that many choices of high-quality and acceptable foods are available in stores and restaurants.

A few general dietary changes underlie implementation of the Step-One Diet. To decrease intake of total fat, saturated fatty acids, and cholesterol, attention should be given to reducing foods containing butter fat—butter itself, cheese, ice cream, cream, whole (4%) milk, and even 2% milk. Only lean cuts of meat should be selected, visible fat should be trimmed away, and fat should be allowed to drain from meat after cooking. The skin of chicken should be removed, and fish should be substituted frequently for meat. Consumption of egg yolks and organ meats (liver, brain, sweetbreads) should be reduced. Shrimp, lobster, and other shellfish contain varying amounts of cholesterol but are low in fat, and thus may be eaten occasionally. The vegetable oils rich in saturated fatty acids—coconut oil, palm kernel oil, and palm oil—are used in some commercial foods and food products; products that list these oils as ingredients on the label should generally be avoided.

a. Specific food subgroups.

Special attention should be given to certain common foods in the diet. This subsection provides specific recommendations:

- **Meats.**

  Beef, Pork, and Lamb. Use *lean* cuts of beef, pork, and lamb. Lean cuts of beef include extra-lean ground beef, sirloin tip, round steak, rump roast, arm roast or center-cut ham, loin chops, and tenderloin. Trim all fat off the outside of meats before cooking. It is not necessary to severely curtail the intake of red meat. Lean meat is rich in protein and contains a highly absorbable form of iron. Pre-menopausal women in particular should avoid severe reduction of lean red meat that would increase the risk for iron-deficiency anemia.

  Processed Meats. Eat very little high-fat processed meats—bacon, bologna, salami, sausage, and hot dogs. Processed meats contain large quantities of "hidden" fat, and they are not rich in valuable nutrients.

  Organ Meats. The organ meats—liver, sweetbreads, kidneys, and brain—are very rich in cholesterol, and they should be limited.

  Chicken and Turkey. These are good sources of protein. The fat of poultry should be reduced by removal of skin and underlying fat layers. Chicken and turkey can be substituted for lean red meat in the diet, but they do not contain as much iron. Chicken and poultry should not be fried in fats rich in saturated fatty acids or covered with fat-rich sauces.

TABLE

5.— *Recommended Diet Modifications to Lower Blood Cholesterol: The Step-One Diet*

	Choose	Decrease
Fish, Chicken, Turkey, and Lean Meats	Fish, poultry without skin, lean cuts of beef, lamb, pork or veal, shellfish	Fatty cuts of beef, lamb, pork; spare ribs, organ meats, regular cold cuts, sausage, hot dogs, bacon, sardines, roe
Skim and Low-Fat Milk, Cheese, Yogurt, and Dairy Substitutes	Skim or 1% fat milk (liquid, powdered, evaporated) Buttermilk	Whole milk (4% fat): regular, evaporated, condensed; cream, half and half, 2% milk, imitation milk products, most nondairy creamers, whipped toppings
	Nonfat (0% fat) or low-fat yogurt	Whole-milk yogurt
	Low-fat cottage cheese (1% or 2% fat)	Whole-milk cottage cheese (4% fat)
	Low-fat cheeses, farmer, or pot cheeses (all of these should be labeled no more than 2-3 g fat/ounce)	All natural cheeses (e.g. blue, roquefort, camembert, cheddar, swiss)
		Low-fat or "Light" cream cheese, low-fat or "Light" sour cream
		Cream cheeses, sour cream
	Sherbet Sorbet	Ice cream
Eggs	Egg whites (2 whites=1 whole egg in recipes), cholesterol-free egg substitutes	Egg yolks
Fruits and Vegetables	Fresh, frozen, canned, or dried fruits and vegetables	Vegetables prepared in butter, cream, or other sauces
Breads and Cereals	Homemade baked goods using unsaturated oils sparingly, angel food cake, low-fat crackers, low-fat cookies	Commercial baked goods: pies, cakes, doughnuts, croissants, pastries, muffins, biscuits, high-fat crackers, high-fat cookies
	Rice, pasta	Egg noodles
	Whole-grain breads and cereals (oatmeal, whole wheat, rye, bran, multigrain, etc.)	Breads in which eggs are major ingredient
Fats and Oils	Baking cocoa	Chocolate
	Unsaturated vegetable oils: corn, olive, rapeseed (canola oil), safflower, sesame, soybean, sunflower	Butter, coconut oil, palm oil, palm kernel oil, lard, bacon fat
	Margarine or shortening made from one of the unsaturated oils listed above	
	Diet margarine	
	Mayonnaise, salad dressings made with unsaturated oils listed above	Dressings made with egg yolk
	Low-fat dressings	
	Seeds and nuts	Coconut

TABLE

6.— *Cholesterol and Fat Content of Animal Products in Three Ounce Portions (Cooked)*

Source	Cholesterol Content mg/3 oz.	Total Fat Content g/3 oz.
Red Meats (lean)		
Beef	77	8.7
Lamb	78	8.8
Pork	79	11.1
Veal	128	4.7
Organ Meats		
Liver	270	4.0
Pancreas (sweetbreads)	400	2.8
Kidney	328	2.9
Brains	1,746	10.7
Heart	184	4.8
Poultry		
Chicken (without skin)		
light	72	3.8
dark	79	8.2
Turkey (without skin)		
light	59	1.3
dark	72	6.1
Fish		
Salmon	74	9.3
Tuna, light canned in water	55	0.7
Shellfish		
Abalone	80	0.8
Clams	57	1.7
Crab meat		
Alaskan King	45	1.3
Blue Crab	85	1.5
Lobster	61	0.5
Oysters	83	4.2
Scallops	35	0.8
Shrimp	166	0.9

Fish. Fish are a good source of protein. They contain cholesterol, but usually are low in saturated fatty acids. The preparation of fish is important. Like chicken and turkey, they should not be fried in saturated fats or covered with fat-rich sauces.

Shellfish. Most shellfish contain less fat than meat and poultry. Their cholesterol content is variable (see Table 6). Some shellfish (e.g., shrimp) are relatively high in cholesterol, but even these can be eaten occasionally within the recommended guidelines for cholesterol intake.

A reasonable approach to meat consumption is to limit intake of lean meat, chicken, turkey, and fish to 6 ounces per day. The cholesterol and total fat content per 3 ounces (the recommended portion size) of various cooked meats are presented in Table 6.

- **Dairy Products.**
  Use skim milk or 1% milk instead of 2% or whole milk, which contains approximately 4% fat. Decrease natural and processed cheeses; substitute low-fat (2%) cottage cheese or synthetic cheeses produced from vegetable oils. Choose yogurt of the nonfat or low-fat (1-2%) type. Experiment with evaporated skim milk in recipes calling for heavy cream. Substitute low-fat yogurt or low-fat cottage cheese for sour cream in dips and salad dressings. Have at least 2 servings of very low-fat dairy products, such as 2 glasses of skim (or 1%) milk, daily to help maintain calcium intake.

- **Fats and Oils.**
  The general rule is to reduce intakes of fats and oils that are high in saturated fatty acids and cholesterol. Butter fat is high in both and should be curtailed as much as possible. Lard and beef fat are other blood cholesterol-raising animal fats. Vegetable fats do not contain cholesterol. However, certain vegetable fats—coconut oil, palm oil, and palm kernel oil—are very high in saturates and should be avoided; these fats are often used in bakery goods, processed foods, popcorn oils, and nondairy creamers. Labels on these foods should be read carefully to detect the presence of saturated vegetable oils.

  Unsaturated vegetable oils and fats do not raise blood cholesterol, but they should be limited because they are high in calories. Generally, up to 6 to 8 teaspoons a day is acceptable. Desirable liquid vegetable oils are corn oil, cottonseed oil, olive oil, rapeseed (canola) oil, safflower oil, soybean oil, and sunflower oil. Peanut oil is less desirable, but small amounts are acceptable. Margarine represents partially hydrogenated vegetable oil and is preferable to butter. Vegetable shortenings fall into the same category as margarine. Both contain quantities of *trans* fatty acids; these are not naturally occurring and should not be taken in excess. Mayonnaise and salad dressings often are made from unsaturated fats, but they too should be limited because of their high caloric content.

- **Eggs.**
  Eat no more than three egg yolks in a week on the Step-One Diet, and no more than one per week on the Step-Two Diet. Egg yolks often are hidden in cooked

and processed foods. Egg whites contain no cholesterol, and they can be eaten often. Experiment with 1-2 egg whites instead of whole eggs in recipes, or use commercial egg substitutes that do not contain yolk.

- **Fruits and vegetables.**
  It is advisable to feature fruits and vegetables as an important part of each meal. Both are rich in vitamins, fiber, and some minerals and contribute to achieving the recommended allowances of these nutrients. Certain green and yellow vegetables may reduce the risk for cancer. Fruits (and even vegetables) can be used for snacks and desserts.

- **Breads, cereals, pasta, rice, dried peas, and beans.**
  These products are high in carbohydrate and protein and most are low in fat. Therefore, they can be increased in the diet as substitutes for fatty foods. However, they too contain calories and must not be eaten in excess. Cereals can be eaten as snacks as well as for breakfast. Dried peas and beans are good sources of protein. Combine large quantities of pasta, rice, legumes, and vegetables with smaller amounts of lean meat, fish or poultry to derive complete protein sources with less fat and calories.

- **Nuts.**
  Nuts tend to be high in fat, but the fat usually is unsaturated. The intake of nuts should thus be limited mainly to avoid excess calories. The same is largely true for peanut butter.

b. Other eating tips.

- **Snacks.**
  Most candies should be limited as snacks; they tend to be rich in simple sugars and fats, and their caloric content outweighs their nutritional value. Some good choices in snacks are graham crackers, rye krisp, melba toast, soda crackers, bagels, English muffins, fruit, ready-to-eat cereals, and vegetables; these are preferable to snack crackers, french fries, and chips. Popcorn should be air popped or cooked in small amounts of liquid vegetable oil.

- **Desserts.**
  Eat fruits, low-fat fruit yogurt, and fruit ices instead of pastries, cake, and cookies. Also acceptable are sherbet, angel food cake, jello, frozen low-fat yogurt, and occasionally ice milk.

- **Cooking methods.**
  Choose those methods that use little or no fat. They include steaming, baking, broiling, grilling, or stir-frying in small amounts of fat. Foods can be cooked in the microwave or in a nonstick pan without added fat. Limit fried foods and avoid frying in saturated fat. Soups and stews should be chilled after cooking, and the congealed fat that forms on top after a few hours in the refrigerator should be skimmed off. When preparing meals avoid use of excess sodium which can contribute to raising blood pressure in some people.

- **Eating away from home.**
  Order entrees, potatoes, and vegetables without sauces or butter. When meat

exceeds the size of a deck of cards (3-4 ounces), the rest can be taken home for another meal. Choose vegetable or fruit salads, and ask for salad dressings to be served on the side; use dressings sparingly. Limit high-fat toppings such as bacon, crumbled eggs, cheese, sunflower seeds, and olives—the latter two because they may be high in fat and salt. Ask for margarine instead of butter, and limit amounts of margarine used on bread and baked potatoes.

The physician who follows patients with high blood cholesterol frequently will be asked about specific food items. It may be helpful for the physician to have available a reference on food composition (see references 48 and 49).

3. *Behavioral Modification.*

Long-term adherence to the recommended diets can be achieved only through permanent modification of eating behavior. Several factors are required to achieve long-term success in adapting to a new diet. The rationale for diet change can be provided by the physician. Education of the patient in the principles of the fat-modified diet is the responsibility of the physician, the physician's immediate staff (e.g., nurses), and when utilized, a registered dietitian. The effectiveness of this approach will be facilitated by frequent communication among the different members of the team. Followup and monitoring by physicians is a key element in achieving the goals of LDL lowering on a long-term basis. Sometimes, permanent modification of eating behavior will require prolonged interaction with a registered dietitian. A brief summary of the process of dietary instruction and behavior modification as practiced by dietitians is provided in Appendix III. This discussion may guide physicians in their own instructions to the patient.

An important adjunct to long-term change in eating behavior and lifestyle is a regular exercise program. Especially useful forms of exercise are activities that require movement of the body over distance—walking, stair climbing, running, cycling, and swimming. Improvements in cardiovascular fitness result from exercising regularly at moderate intensity for 15 to 30 minutes at least every other day. However, vigorous exercise must be carried out with caution in high-risk persons, and only with the advice of a physician and under the supervision of trained personnel.

E. *Monitoring and Followup*

1. *Step-One Diet.*

After starting the Step-One Diet, the serum total cholesterol level should be measured at 4-6 weeks and at 3 months (see Figure 5). This will allow the patient enough time to adopt new eating habits and to respond to the dietary change. At

the end of 3 months, the physician should assess the patient's adherence to the diet plan and response to dietary therapy. The response can be judged on the basis of the change in serum cholesterol level. If the response is satisfactory, i.e., if the total cholesterol monitoring goal is met (<240 mg/dl without definite CHD or two other risk factors, <200 mg/dl with definite CHD or two other risk factors—see Table 2), then the LDL-cholesterol level should be measured in order to confirm that the LDL-cholesterol goal has been met. If the LDL goal is met, the phase of long-term monitoring can begin. If the response is not satisfactory, the patient should generally be referred to a registered dietitian and should progress to the Step-Two Diet or to another trial on the Step-One Diet. If this latter approach is selected, the patient should again be evaluated after 4-6 weeks and 3 months, with progression to the Step-Two Diet if the response is still not satisfactory.

2. *Step-Two Diet.*

On the Step-Two Diet, serum cholesterol levels should be measured after 3-4 weeks and 3 months of therapy. After 3 months of treatment with the Step-Two Diet, the physician should again assess the patient's adherence and response to the diet. It is important to document the extent of adherence to the therapeutic diet. If the desired goal for serum cholesterol-lowering has been attained, and a measurement of LDL-cholesterol level confirms that the LDL goal has been met, long-term monitoring can begin; if not, consideration should be given to drug therapy.

3. *Diet Success: Long-Term Monitoring.*

The patient who has achieved the target goals for lowering of LDL-cholesterol by dietary therapy can be declared a diet success. Monitoring of total cholesterol should be carried out on a long-term basis. The fat-modified diet should be maintained indefinitely and the patient should be encouraged to adhere to the recommended eating pattern. Diet education should be continued and reinforced, by a registered dietitian if necessary. The patient should be counseled quarterly for the first year of long-term monitoring and twice yearly thereafter.

Total serum cholesterol should be measured prior to each visit, and the results should be used at the counseling session. For patients who have no lipoprotein abnormalities other than elevated LDL-cholesterol, monitoring at 6-month intervals is appropriate. In such patients, the total cholesterol measurement, which can be made with a nonfasting blood sample and is less expensive than lipoprotein analysis, will provide a reasonable index of the LDL-cholesterol level. Many patients who previously have had high cholesterol levels on the typical American diet are "diet sensitive," which explains their originally high level. This means that continuous attention must be given to dietary adherence to avoid a "relapse" to high cholesterol concentrations. If the patient redevelops an elevated cholesterol level, the procedure outlined above for dietary therapy of elevated LDL-cholesterol may have to be reinstituted.

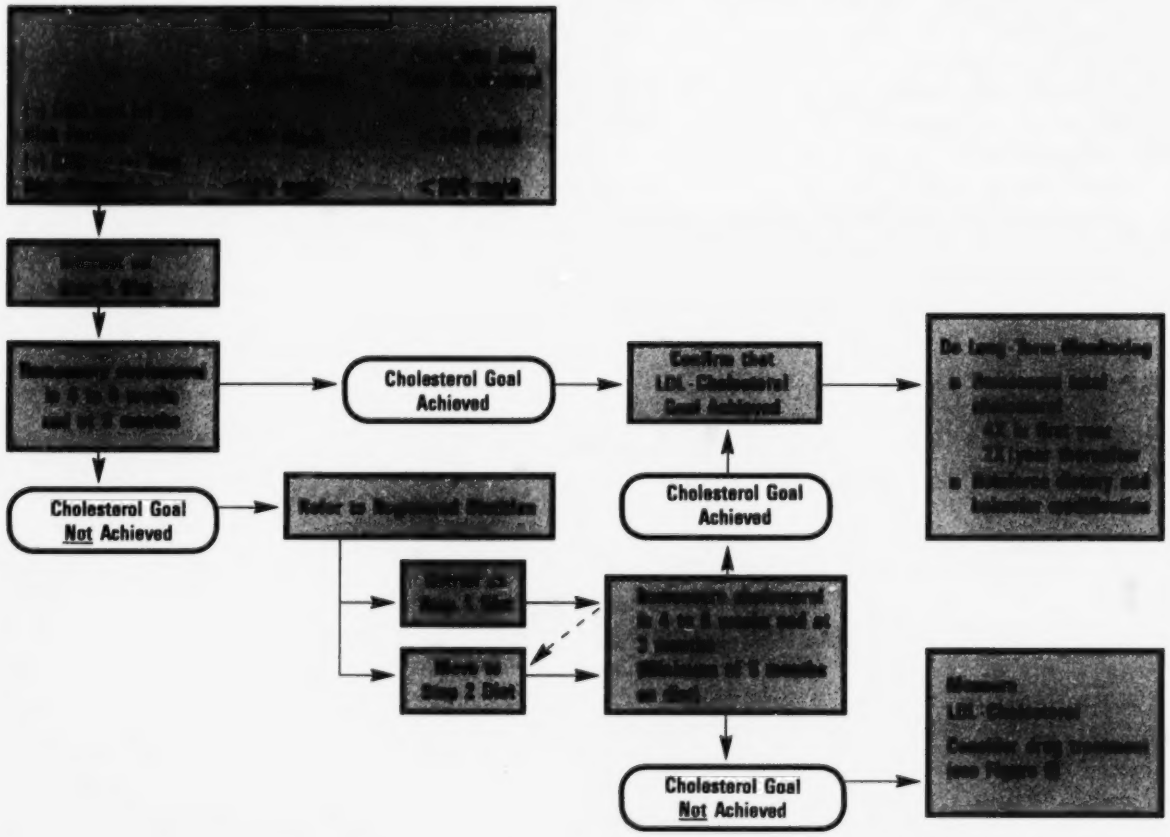
4. *Inadequate Response to Diet.*

A patient who fails to achieve the goals for lowering of total cholesterol (or LDL-cholesterol) by dietary therapy should be classified as having an inadequate response to diet. This does not necessarily mean diet failure, because a significant reduction in cholesterol levels may have occurred by diet modification. There are four categories of inadequate response to diet that can be distinguished.

(1) Patients who have severe elevations of serum cholesterol often cannot achieve the goals of serum cholesterol lowering by diet, no matter how strict the diet. For these patients (see Appendix II), it is not necessary to wait for six months of dietary therapy before adding drugs to the regimen.

FIGURE

5 – *Dietary Treatment*



*One of which can be male sex (Table 2).

(2) Some patients with high LDL-cholesterol levels are biologically relatively resistant to LDL lowering by diet modification and will not achieve the cholesterol lowering goal despite good adherence to diet.

(3) Others will adhere poorly to diet in spite of an intensive effort by the physician and counselors. After a few months it will be obvious that these patients will not adhere to dietary recommendations. Some physicians have the mistaken belief that most patients fall into this category, but this certainly is not true. A concerted effort by the physician, immediate staff, and registered dietitian should minimize the size of this group of patients.

(4) For still other patients, a more prolonged period of dietary therapy may be justified. Up to a year, or even longer, may be required for a patient to learn to modify the diet by changing both the pattern of diet and eating habits. There may be a tendency for some physicians to employ drugs too soon instead of making the effort to change the patient's dietary habits. This tendency must be resisted. Adequate time should be allowed for the patient to attempt to modify the diet to achieve the desired goals of therapy.

F. *Dietary Therapy for Special Groups*

1. *Severe Primary and Secondary Lipid Disorders.*

Patients with severe primary hypercholesterolemia (e.g., familial hypercholesterolemia) deserve maximal dietary therapy, i.e., the Step-Two Diet. However, many of these patients will not respond adequately to diet and will require drug therapy (see Appendix II). Patients with severe primary hypertriglyceridemia should receive special attention to dietary management, which is described in more detail in Appendix II. The role of the diet in the treatment of low HDL-cholesterol and diabetic dyslipidemia likewise is discussed in Appendix II.

2. *Elderly High-Risk Patients.*

When considering dietary therapy for elderly patients classified as high risk, the value of diet modification for prevention of atherosclerotic disease must be balanced against the possibility of inadequate or inappropriate nutrition, which is often a problem in the elderly. The Step-One Diet seems prudent in elderly patients classified as high risk, but overly restrictive diets probably should be avoided. Intensive dietary therapy (e.g., the Step-Two Diet) is not advisable in most elderly patients. Sound clinical judgment is required in making a decision about diet modification in older individuals classified as high risk, particularly because adequate intakes of calories and protein can be a major problem among the elderly.

3. *Pregnant Women.*

Elevations in cholesterol and triglyceride levels occur during pregnancy, with

maximum levels in the third trimester. These increased levels are not generally clinically significant, but rare cases of hypertriglyceridemia and pancreatitis have been reported. Thus, some investigators recommend that serum triglyceride levels be measured at about the 28th week of gestation. Triglyceride levels generally return to baseline within 6 weeks postpartum, but elevations in LDL-cholesterol may occasionally persist for 6-9 months. Such a response may represent a predisposition to elevated cholesterol. The approach to hyperlipidemic women who become pregnant is discussed in Appendix II.

G. *Approach To Borderline-High Blood Cholesterol Group*

1. *Assessment of Risk.*

Individuals with cholesterol levels in the range of 200-239 mg/dl are classified as having borderline-high blood cholesterol. Several studies indicate that cholesterol concentrations in the borderline-high range impart an increased CHD risk as compared to lower levels. However, while there is a progressive increase in risk as the blood cholesterol rises from 200 to 240 mg/dl, the absolute risk does not rise sharply if no other risk factors are present (see Table 1, Background Section). For this reason, it is not necessary to enter most people with borderline-high blood cholesterol into active medical therapy. They nonetheless deserve to receive dietary information and cholesterol education as discussed below.

Special attention should be given to young adults with borderline-high blood cholesterol because they may be "tracking" toward the high-risk category later in life. In fact, many experts believe that young adults (20-39 years of age) with borderline-high cholesterol levels warrant full evaluation of serum lipoprotein fractions. This is an area where individualized clinical judgment is appropriate.

As with all patients, those with borderline-high blood cholesterol levels should be evaluated for other CHD risk factors and should be given preventive medical care for these factors if present. As indicated previously, patients in the borderline-high cholesterol group who have definite CHD or two other CHD risk factors (one of which can be male sex) should be managed in the same way as patients with high blood cholesterol levels.

Some experts believe that patients in the borderline-high cholesterol group who have one other major risk factor (e.g., hypertension) also warrant lipoprotein measurements and possible dietary therapy. This is particularly so for young adults. Although this is not recommended here as a general approach for most patients with borderline-high blood cholesterol, it is clear that individualized clinical judgment and patient management is appropriate for this group.

2. *Dietary Information and Patient Education.*

For individuals with borderline-high blood cholesterol, intensive dietary therapy is not required. The population-based approach for lowering cholesterol levels in the entire community is expected, however, to have a significant impact on the diet and behavior of this group. Since these people are at increased risk for CHD, compared to individuals whose cholesterol levels are below 200 mg/dl, they should be made aware of the significance of their moderately increased risk and given information about how to modify the diet to lower the cholesterol level. The basic recommendation is for the patient to adopt an eating pattern similar to that of the Step-One Diet.

The same materials provided with the Step-One Diet might be made available to these patients by the physician and immediate staff, but intensive monitoring is not required. It should not be necessary to refer the patient to a registered dietitian, and the time devoted to patient instruction will be less than for the high-risk group. It is the physician's responsibility to inform the patient of his or her moderately increased risk, to advise changes in lifestyle and eating habits, to provide educational materials about diet, and to direct the individual to other sources of educational material. For instance, the local chapter of the American Heart Association usually stocks valuable materials containing dietary advice and practical approaches to diet modification. Sections of this report also can be copied for the patient.

Special attention should be given to dietary counseling of young adults with borderline-high cholesterol levels. They should be started on the Step-One Diet, but in addition, they should be monitored for adherence and response more carefully than middle-aged patients in the same category. Young adults should be counseled on what to eat when away from home, and they should develop exercise habits that will be particularly useful as lifetime habits. Young adults who have an exceptionally high caloric intake because of a high level of exercise should be cautioned against excessive intake of saturated fatty acids, cholesterol, and protein.

3. *Reevaluation.*

At the least, a followup measurement of the patient's cholesterol level should be made at 1 year and then at 1-2 year intervals. More frequent followup or measurements of lipoprotein fractions can be made at the discretion of the physician. Extra attention should be given to the followup of young adults with borderline-high blood cholesterol. Periodic determinations of serum cholesterol will indicate the physician's heightened and continuing concern; knowledge that the cholesterol level will be checked periodically should motivate the patient to adhere to the recommended diet; and these measurements will enable the physician to detect an increase in cholesterol level to the high blood cholesterol range, should it occur.

A. When To Consider Drug Therapy: Treatment Goals

1. *LDL-Cholesterol Levels for Initiation of Drug Therapy.*

Patients whose LDL-cholesterol levels remain high despite adequate dietary therapy should be considered for drug treatment. At least 6 months of intensive dietary therapy and counseling should usually be carried out before initiating drug therapy. In individuals with severe elevations of LDL-cholesterol [>225 mg/dl (>5.8 mmol/L)] or with definite CHD, in whom dietary therapy alone is unlikely to be adequate or in whom the urgency of achieving substantial cholesterol lowering is greater, it may be appropriate to try dietary therapy alone for a period shorter than six months before considering drug therapy. A minimum of three months of dietary therapy is required to establish an adequate baseline for evaluating the efficacy of subsequent drug therapy. A registered dietitian, working with the physician to design an adequate treatment plan and assess dietary adherence, may enhance the effectiveness of dietary therapy sufficiently to obviate the need for drugs.

The LDL-cholesterol levels at which drug therapy should be considered after an adequate trial of dietary therapy alone are as follows:

- ≥190 mg/dl (very high-risk LDL-cholesterol): In patients without definite CHD or two other CHD risk factors (one of which can be male sex, see Table 2).
- ≥160 mg/dl (high-risk LDL-cholesterol): In patients with definite CHD or two other CHD risk factors (see Table 2).

Clinical judgment is required when using these guidelines to make decisions about initiating drug therapy. All individuals with LDL-cholesterol levels ≥190 mg/dl are candidates for drug therapy, but the need is less pressing in older women. Men with LDL-cholesterol values between 160 and 190 mg/dl who have any other major risk factor generally should receive drug therapy. In women, however, a more conservative approach to drug therapy is appropriate, in view of the fact that the absolute risk of CHD is lower in women than in men. Thus, for women with LDL-cholesterol levels between 160 and 190 mg/dl, two other major risk factors or definite CHD should be present before initiating drug therapy. The distribution of LDL-cholesterol levels in the population is listed in Appendix I. It should be emphasized that maximum dietary therapy would significantly alter this distribution and decrease the percent of both men and women being considered for drug therapy.

Maximal efforts should be made in all patients to lower cholesterol levels and CHD risk by nonpharmacological approaches, such as diet, weight control, exercise, and other lifestyle modifications (e.g., quitting smoking). This is especially important in patients who have not reached their minimal LDL-cholesterol goal on dietary therapy alone, but who do not qualify for drug treatment according to the above guidelines. These patients include those without definite CHD or two other risk factors (see Table 2) whose LDL-cholesterol levels are in the range of 160-

190 mg/dl, and those with definite CHD or two other risk factors whose LDL-cholesterol levels are 130-160 mg/dl, on adequate dietary therapy. While drug therapy is not routinely recommended for such patients, consideration should be given to the use of low doses of bile acid sequestrants, especially in men. The sequestrants have a proven record of long-term safety. Moreover, many experts feel that patients with definite CHD should receive drug therapy if their minimal LDL-cholesterol goal (<130 mg/dl) has not been reached.

LDL-cholesterol is the best parameter to use in making the decision to use drugs and for monitoring the response to drug therapy (at least in the first few months). The decision to initiate drug treatment usually commits the patient to long-term therapy, for years or even for life. Since the number of potential patients who are candidates for prolonged administration of drugs is substantial, all decisions to initiate drug therapy must be made only after careful deliberation. Dietary therapy is clearly the safest treatment available. Hence, maximal efforts at dietary therapy should be made before initiating drug therapy, and should be continued even if drug therapy is needed.

2. *Target Treatment Levels of LDL-Cholesterol.*

The minimal goals of drug therapy are the same as those of dietary therapy, and are as follows:

- LDL-cholesterol < 160 mg/dl: In patients without definite CHD or two other CHD risk factors (one of which can be male sex, see Table 2).
- LDL-cholesterol <130 mg/dl: In patients with definite CHD or two other CHD risk factors (see Table 2).

The LDL-cholesterol level that is necessary to promote substantial or maximal atherosclerotic regression has not been established, but some investigators believe that an LDL-cholesterol as low as 100 mg/dl (2.6 mmol/L) may be considered an ideal goal. Thus, it may be desirable to strive for an LDL-cholesterol considerably below the minimal target goals of 160 mg/dl or 130 mg/dl, particularly in patients with definite CHD or with other major risk factors, once the decision to institute drug therapy has been made. There is no current evidence or opinion to suggest that further lowering of LDL-cholesterol below 100 mg/dl will produce significant additional benefit.

B. Selection and Use of Drugs

1. *Overview and General Approach.*

The major drugs for consideration include:

- Bile acid sequestrants (cholestyramine, colestipol)

- Nicotinic acid
- HMG CoA reductase inhibitors (lovastatin)
- Gemfibrozil
- Probucol

A brief summary of the major characteristics of these drugs is provided in Tables 7 and 8.

The drugs of first choice for patients without concurrent hypertriglyceridemia [triglyceride <250 mg/dl (<2.8 mmol/L)] are the bile acid sequestrants and nicotinic acid. These drugs have been found to reduce CHD risk and to be generally safe in long-term use. They are effective in lowering LDL-cholesterol. Nicotinic acid is preferred for patients with concurrent hypertriglyceridemia (triglyceride ≥250 mg/dl), because it lowers LDL-cholesterol without exacerbating the hypertriglyceridemia. The bile acid sequestrants can also effectively lower LDL-cholesterol in these patients, but their administration as single drug therapy will sometimes cause substantial increases in serum triglycerides.

TABLE 7.— *Summary of the Major Drugs for Consideration*

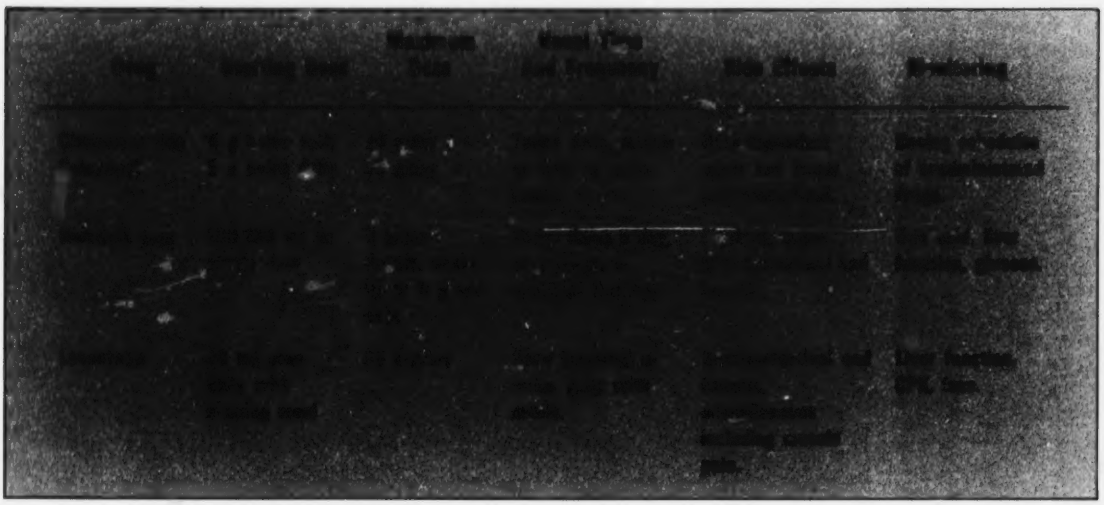
Drugs	Reduces CHD Risk	Long-Term Safety	Maintaining Adherence	LDL-Cholesterol Lowering	Special Precautions
Cholestyramine Colestipol	Yes	Yes	Requires considerable education	15-30%	Can alter absorption of other drugs. Can increase triglyceride levels and should not be used in patients with hypertriglyceridemia.
Nicotinic acid	Yes	Yes	Requires considerable education	15-30%	Test for hyperuricemia, hyperglycemia, and liver function abnormalities.
Lovastatin*	Not proven	Not established	Relatively easy	25-45%	Monitor for liver function abnormalities, and possible lens opacities.
Gemfibrozil[5]	Not proven	Preliminary evidence	Relatively easy	5-15%	May increase LDL-cholesterol in hypertriglyceridemia patients. Should not be used in patients with gallbladder disease.
Probucol	Not proven	Not established	Relatively easy	10-15%	Lowers HDL-cholesterol; significance of this has not been established. Prolongs QT interval.

*Recently approved by the FDA for marketing.

[5]Not FDA approved for routine use in lowering cholesterol. The results of the Helsinki Heart Study should be available soon to define the effect on CHD risk and long-term safety.

TABLE

8. — *Drugs Highly Effective in Lowering LDL-Cholesterol*



Lovastatin is the first available drug in a new class, the HMG CoA reductase inhibitors. It is very effective in lowering LDL-cholesterol levels, produces modest reductions in triglyceride levels, and is easy to administer. The clinical use of lovastatin has been under study for only a few years, and its long-term safety and effects on CHD endpoints have not yet been established. It is therefore not classed as a drug of first choice in this report, and some caution is appropriate in its use.

Gemfibrozil and probucol are other available drugs that are also not classified as drugs of first choice. These drugs are generally not as effective in lowering LDL-cholesterol as are the bile acid sequestrants, nicotinic acid, or the HMG CoA reductase inhibitors. Moreover, these drugs have not been shown to reduce CHD risk and their safety for long-term use has not been established at this time. However, the results of a large clinical trial, the Helsinki Heart Study, evaluating the effects of gemfibrozil on CHD risk are expected soon (59). If a clinically beneficial effect is seen, the recommended use of gemfibrozil will probably be expanded.

The cost of drugs may also warrant consideration. Cost should be viewed in relation to a drug's effectiveness and safety in cholesterol lowering. The following are the approximate yearly wholesale costs of drugs, derived from data in the 1986 Redbook; retail costs will be somewhat higher. Cholestyramine (Questran) at a daily dose of 16 g or colestipol (Colestid) at a daily dose of 20 g in bulk containers is $500-550; "generic" nicotinic acid at a daily dose of 3 g is $50, while Nico-Bid is $700; gemfibrozil (Lopid) at a daily dose of 1.2 g or probucol (Lorelco) at a daily dose of 1 g is approximately $375. Lovastatin is being marketed to the pharmacist at $1.25 per 20 mg tablet; at a dose of 40 mg/day, the yearly wholesale cost will be approximately $910.

Many patients with marked elevations of LDL-cholesterol will not be adequately controlled with single drug therapy, and the use of combinations of drugs with synergistic mechanisms of action may be particularly effective in these patients. The mechanisms of action, clinical efficacy, and side effects of the drugs of first choice and the HMG CoA reductase inhibitors for the treatment of high-risk LDL-cholesterol levels are discussed in the following section. There then follows a more abbreviated discussion of the other drugs and of combination drug therapy.

2. *Drugs of First Choice.*

a. Bile acid sequestrants: cholestyramine and colestipol.

The major effect of the bile acid sequestrants is a lowering of the level of LDL-cholesterol. The sequestrants have the advantage that their use has been shown to reduce CHD risk in large-scale intervention trials and that long-term safety information is also available (10,13). The sequestrants are not absorbed from the gastrointestinal tract and lack systemic toxicity. Thus, they are particularly suitable for treating younger patients, especially children and women considering pregnancy. The disadvantages of the sequestrants are related to the method of administration and the frequency of gastrointestinal side effects.

The primary action of the sequestrants, which are anion exchange resins, is to bind bile acids in the intestinal lumen; this interrupts the enterohepatic circulation of bile acids and leads to an increased hepatic synthesis of bile acids from cholesterol. Depletion of the hepatic pool of cholesterol results in an increase in LDL receptor activity in the liver. This in turn stimulates removal of LDL from plasma and lowers the concentration of LDL-cholesterol. Bile acid sequestrant therapy may increase hepatic VLDL production and thus increase the plasma concentration of triglycerides.

Cholestyramine and colestipol are both powders that must be mixed with water or fruit juice; they are taken in two (or occasionally three) divided doses with meals. The cholesterol-lowering effects of 4 g of cholestyramine are equivalent to those obtained with 5 g of colestipol. Decreases in LDL-cholesterol of 10-15% may be achieved with the initial suggested starting dosage schedule of 5 g of colestipol (or 4 g of cholestyramine) taken twice daily. In patients who do not respond adequately, the dose is increased gradually. Generally, the benefits of daily doses exceeding the equivalent of 16 g of cholestyramine are offset by poorer patient adherence and a greater incidence of gastrointestinal side effects. The response to therapy in individual patients is quite variable but 15-30% reductions in the concentrations of LDL-cholesterol may be achieved with 16-24 g/day of cholestyramine or an equivalent dose of colestipol. The choice of one or the other of these drugs is dependent on individual patient preference based on taste and palatability. Cholestyramine is available in 9 g packets (each containing 4 g of cholestyramine and 5 g of orange flavored filler) and in 378 g cans. Colestipol is available in 5 g packets and bottles containing 500 g, and there are no additives.

The cost-per-unit dosage for cholestyramine is currently considerably less when it is purchased in bulk containers.

The bile acid sequestrants are contraindicated as single-drug therapy in patients with marked hypertriglyceridemia [triglyceride >500 mg/dl (>5.7 mmol/L)] or patients with a history of severe constipation. The most common side effects associated with sequestrant therapy are gastrointestinal, and include constipation, bloating, epigastric fullness, nausea, and flatulence. Some suggestions for dealing with these side effects are provided in Appendix IV. These drugs are not absorbed, but they may interfere with the absorption of other anionic drugs if these are taken concurrently. It is generally advisable to take other medications at least 1 hour before or 4 hours after the bile acid sequestrants. The sequestrants can interfere with the absorption of digitoxin, warfarin, thyroxine, thiazide diuretics, beta blockers, and potentially many other drugs. Decreased absorption of fat-soluble vitamins and folic acid has been reported with prolonged high doses of the resins, primarily in patients with severe liver or small bowel disease. Routine vitamin supplementation is not needed or recommended in adult patients. Biochemical side effects include a modest increase in plasma triglyceride concentrations in many patients and an occasional mild and usually transient increase in alkaline phosphatase and transaminase.

b. Nicotinic acid.

The water-soluble B vitamin, nicotinic acid, has been used to lower plasma lipid levels for many years. Administration of nicotinic acid in the Coronary Drug Project was associated with a reduction in recurrent myocardial infarctions and in long-term total mortality (11,53). Nicotinic acid lowers total and LDL-cholesterol and triglycerides and raises HDL-cholesterol levels. Decreases in total cholesterol levels of 25% may be observed. Nicotinic acid decreases the hepatic production of VLDL, and ultimately the production of LDL-cholesterol. Nicotinamide is not effective in lowering LDL-cholesterol and can not substitute for nicotinic acid.

Nicotinic acid is a very effective drug which requires considerable physician and patient education (see Appendix IV). Although it has frequent side effects, these are generally reversible upon reducing the dose or discontinuing the drug. Because of its proven efficacy and safety, the efforts required to use this agent are justified.

Nicotinic acid is the least costly of all the currently available agents. Side effects, especially flushing of the skin, often limit acceptance by patients. The flushing is prostaglandin mediated and can be significantly decreased by pretreatment with aspirin or nonsteroidal anti-inflammatory drugs. Tolerance to this flushing develops rapidly over several weeks. Flushing is greatly reduced by slowly increasing nicotinic acid to full dose and avoiding administration on an empty stomach. The use of sustained-release preparations will also reduce flushing, but the cost is considerably greater (54). Flushing will return if doses are omitted from the prescribed schedule.

Nicotinic acid therapy is generally initiated with a single dose of 100-250 mg/day.

This initial dose is usually given after dinner to minimize problems with flushing during normal daily activities. The frequency of dose and total daily dose is slowly increased every 4-7 days until the first-level therapeutic dose of 1.5-2 g/day is reached. If the LDL-cholesterol is not lowered sufficiently, the dose should be increased to 3 g/day (1.0 g three times/day). In patients with marked elevations of plasma cholesterol, a higher daily dose up to 6 g/day is occasionally used.

Hyperuricemia and abnormalities in liver function studies are other common adverse effects, but are more likely with higher doses of nicotinic acid. Hyperglycemia and a number of gastrointestinal side effects occasionally occur. Liver function, blood glucose, and uric acid levels should be evaluated before beginning nicotinic acid and after reaching therapeutic dosage or increasing the dose level. The medication is supplied in 50-, 100-, and 500-mg tablets. The latter dosage is preferred for chronic therapy. Contraindications to nicotinic acid therapy include peptic ulcer, hepatic disease, and gouty arthritis or significant hyperuricemia.

3. *New Drugs: Inhibitors of HMG CoA Reductase.*

The discovery of specific competitive inhibitors of the rate-limiting enzyme in cholesterol biosynthesis (HMG CoA reductase) has opened up a new avenue of therapy for patients with primary hypercholesterolemia (55,56). A number of drugs in this category are currently being evaluated including lovastatin, simvastatin, and pravastatin. Of these, lovastatin has been most extensively studied in humans and has recently been approved for marketing. Long-term safety information is limited or not available, and thus caution in its use is recommended. This is especially true for individuals who are not at high risk.

Although the effects of HMG CoA reductase inhibitors on CHD incidence have not yet been established, mean reductions in LDL-cholesterol of 25-45% have been noted in both familial and nonfamilial forms of hypercholesterolemia. HMG CoA reductase inhibitors increase LDL receptor activity in the liver and increase the rate of receptor-mediated removal of LDL from plasma. Additionally, the production of LDL is also decreased. Patients are generally started on 20 mg of lovastatin once daily with the evening meal. The dose may be increased to 40 and then to 80 mg/day as a single evening dose or divided (b.i.d.) doses with meals. The cholesterol-lowering effects of lovastatin have persisted for the duration of the observed treatment periods up to 2-4 years.

Lovastatin at doses of 20 to 80 mg daily has been well tolerated. Reported side effects (often transient) to date have included changes in bowel function, headaches, nausea, fatigue, insomnia, skin rashes, and myositis (myalgia associated with markedly elevated CPK levels), which collectively have occurred in less than 5% of treated patients. Biochemical changes have included increases in transaminases and CPK. Approximately 1.9% of patients have developed persistent increases in transaminase levels of greater than 3 times normal after 3-16 months of therapy requiring discontinuance of therapy. Careful monitoring of liver function studies is essential. Lovastatin does not impair steroid hormone production. There is a

concern about the possibility that there may be effects on formation of lens opacities; although no effects have been detected to date in humans, this is still being investigated. Baseline and regular follow-up evaluation of the lens should be done.

If long-term safety can be satisfactorily established, these inhibitors of cholesterol biosynthesis will represent a major advance in the therapy of hypercholesterolemia. These agents are extremely effective in reducing LDL-cholesterol concentrations and, from the patient's point of view, are easy to take.

4. *Other Drugs.*

a. Gemfibrozil.

Gemfibrozil, a fibric acid derivative, is approved by the Food and Drug Administration (FDA) primarily for triglyceride lowering to reduce the risk of pancreatitis, and not for routine use in lowering cholesterol to reduce the risk of CHD. It is sometimes used as single drug therapy in patients who do not tolerate the resins or nicotinic acid, and is occasionally used in combination with first choice drugs (see Combined Drug Treatment, below). The long-term safety and effects of gemfibrozil on CHD risk are still being evaluated in clinical trials. Preliminary evidence for long-term safety of gemfibrozil is available in the interim report of the Helsinki Heart Study (59). This is a large, placebo-controlled study to evaluate the effect of this drug on CHD risk, and the results should be announced in the near future. If a clinically beneficial effect is demonstrated in this clinical trial, the recommended use of gemfibrozil will probably be expanded.¶¶

Gemfibrozil is primarily and highly effective in lowering triglycerides, and there is an associated increase in HDL-cholesterol. Because of the effect of this drug on HDL-cholesterol, the results of the Helsinki Heart Study may be of particular interest. To date, increases of HDL-cholesterol induced by treatment have not been conclusively shown to be associated with a decreased risk of CHD. A decrease in LDL-cholesterol of 10-15% may be seen in patients without elevated triglycerides treated with gemfibrozil. An increase in LDL-cholesterol may be seen in primary hypertriglyceridemia, and either increases or decreases in LDL-cholesterol may be seen in patients with elevated levels of both cholesterol and triglycerides. Gemfibrozil is well tolerated in most patients. The more common side effects include a variety of gastrointestinal symptoms, and occasional changes in hematological parameters and liver function tests are noted. Gemfibrozil potentiates the effects of oral anticoagulants and increases biliary lithogenicity. It is available as 300 mg capsules, and the usual dosage is 600 mg twice daily.

b. Probucol.

Probucol therapy usually reduces LDL-cholesterol by about 8-15%, but there is also an associated reduction in HDL-cholesterol of up to 25%. There are no extensive, long-term clinical studies currently available for assessing probucol's safety or effect on CHD risk. Preliminary information indicates that probucol may inhibit the oxidation and tissue deposition of LDL. Probucol increases the rate of LDL

¶¶ See Additional Note at the end of this section (page 62).

catabolism, part of which may involve nonreceptor mediated pathways (57). The role of probucol in the treatment of patients with high LDL-cholesterol is uncertain because of concerns about the reduction in HDL-cholesterol, but xanthoma regression has also been reported as the HDL-cholesterol level decreases. Probucol is sometimes used as single drug therapy in patients who do not tolerate other drugs, and is occasionally used in combination with first choice drugs (see Combined Drug Treatment, below).

Probucol is generally well tolerated, and side effects (including diarrhea, flatulence, abdominal pain, and nausea) occur in less than 5% of patients. Probucol causes prolongation of the QT interval, and the drug should be regarded as contraindicated in patients with ECG findings suggestive of ventricular irritability, with an initially prolonged QT interval, or taking other drugs that prolong the QT interval. Probucol is stored in adipose tissue, and blood levels fall slowly after therapy is discontinued. It is available in 250 mg tablets, and the usual dose is 500 mg twice daily.

c. Clofibrate.

Clofibrate, like gemfibrozil, is a fibric acid derivative. It is approved by the FDA primarily for triglyceride lowering to reduce the risk of pancreatitis, and not for routine use in lowering cholesterol to reduce the risk of CHD. Its effects on lipids and lipoproteins and its side effects are generally similar to those described above for gemfibrozil. Clofibrate is used less frequently than gemfibrozil, however, because of reports of long-term toxicity in clinical trials, particularly the WHO Clofibrate Study (58).

5. Miscellaneous Drugs.

These drugs are not recommended for general use.

a. Neomycin.

Neomycin is a nonabsorbable aminoglycoside antibiotic with cholesterol-lowering effects. Reductions in LDL-cholesterol levels of 20-25% have been reported. Side effects include diarrhea and abdominal cramps. Neomycin also has a potential to cause serious ototoxicity and nephrotoxicity. This drug is not FDA approved as a lipid-lowering agent, and its use should be considered investigational.

b. Dextrothyroxine.

Dextrothyroxine, the optical isomer of L-thyroxine, moderately lowers the concentrations of LDL-cholesterol but does so at the expense of making the patient moderately hyperthyroid. Dextrothyroxine is approved by the FDA for use in selected young adults with primary hypercholesterolemia who are unable to take other effective lipid lowering drugs. It is not recommended for use in this report because of the high incidence of adverse cardiovascular effects and hypermetabolic effects. Other available drugs have a more favorable benefit/risk ratio.

6. Investigational Drugs.

There is currently a flurry of activity in the development of new cholesterol-

lowering agents. There are several new HMG CoA reductase inhibitors in various stages of development. Simvastatin and pravastatin are currently being extensively investigated in clinical trials. A number of newer fibric acid derivatives are available in Europe, and bezafibrate and fenofibrate have been fairly extensively evaluated in the United States. They appear to be more effective in lowering LDL-cholesterol than gemfibrozil or clofibrate.

7. *Combined Drug Treatment.*

If the response to single-drug therapy with one of the drugs of first choice is inadequate, combined drug therapy using two agents, preferably with synergistic mechanisms of action, should be considered to further lower LDL-cholesterol (12,56,60). Experience with such drug combinations is somewhat limited, and it might be advisable to undertake such combination therapy in consultation with a lipid specialist. In patients without concurrent hypertriglyceridemia, the combination of a bile acid sequestrant with either nicotinic acid or lovastatin has the potential of lowering LDL-cholesterol by 45-60%. The addition of probucol or gemfibrozil to bile acid sequestrant therapy may occasionally be beneficial, but the efficacy of these combinations is significantly less than the above-mentioned combinations. The combination of sequestrants and probucol may result in fewer gastrointestinal complaints.

For patients with both increased LDL-cholesterol levels and hypertriglyceridemia, nicotinic acid and lovastatin represent initial drugs of choice. Lovastatin and nicotinic acid can also be used in combination, or either of these two drugs can be combined with a bile acid sequestrant to obtain a possible additional 20-25% reduction in LDL-cholesterol. As yet, there is very little experience with the combination of lovastatin and nicotinic acid in terms of possible adverse effects such as hepatotoxicity. The addition of gemfibrozil to a bile acid sequestrant, lovastatin, or nicotinic acid will usually produce additional lowering of triglycerides, but the effect on change in LDL-cholesterol levels is quite variable. More experience is required with the combination of lovastatin and gemfibrozil to see if there is an increased risk of myositis.

8. *Other Approaches.*

Effective control of elevated levels of LDL-cholesterol will be attainable in the majority of patients using the primary drugs and drug combinations discussed above. Patients who do not achieve adequate cholesterol reduction after this type of therapy should be referred to a specialist in lipid disorders. In addition to investigational drugs or other drug combinations, other approaches may be indicated. In patients with familial hypercholesterolemia (FH), plasmapheresis (either simple plasma exchange or plasma exchange with some type of affinity chromatography) has been used to selectively remove LDL from plasma. A surgical procedure, partial ileal bypass, has occasionally been used to lower LDL-cholesterol in heterozygous FH. In homozygous FH, portacaval shunt and liver transplant have been employed.

C. *Monitoring and Followup of Patients*

Drug therapy is usually not begun until patients have had at least a 6-month trial of dietary therapy. The decision to begin drug therapy should be reviewed with the patient along with the respective benefits and side effects of the appropriate drugs.

It is important to have a minimum of two determinations of lipoprotein levels during the last 1-2 months of maximum dietary therapy, because the efficacy of drug therapy needs to be judged against an accurately determined baseline. With good drug adherence, maximum lowering of LDL-cholesterol is obtained within 4 weeks of initiating drug therapy. Thus, the first follow-up LDL-cholesterol determination should be made 4-6 weeks after initiating drug therapy. A second measurement should be done at 3 months; a minimum of two lipoprotein determinations is essential for evaluating drug efficacy. The mean of these two determinations and a careful assessment of drug adherence should be used to initially judge the effectiveness of drug treatment. After the response to drug therapy has been established and if the response is adequate, then the patient should be seen for a follow-up visit approximately every 4 months, in order to monitor for side effects and assess the patient's status and response to therapy. A lipoprotein profile (LDL-cholesterol measurement) at yearly intervals will usually be adequate; measurement of serum total cholesterol will usually suffice for the interim visits (see Figure 6). In the course of long-term monitoring, if the total cholesterol or lipoprotein determination at a particular visit is out of keeping with the patient's previous values, a repeat determination should be done to confirm the level.

The previously obtained laboratory work and medical history and physical examination should be reviewed before initiating drug therapy to see if any tests should be repeated or whether additional tests are required. The laboratory indications of adverse drug effects are generally manifested by changes in blood count, or liver or kidney function studies. These tests should definitely be repeated within 1-3 months of initiation of drug therapy, depending upon the drug used, and at 4- to 12-month intervals thereafter. Additional testing may be required if abnormalities are noted, or if a high dose of drug is being used, or because of the known toxicity profile of a given drug (see previous discussion of major adverse effects for individual drugs). For example, more frequent transaminases are indicated when using lovastatin and more frequent uric acid and liver function determinations with higher doses of nicotinic acid.

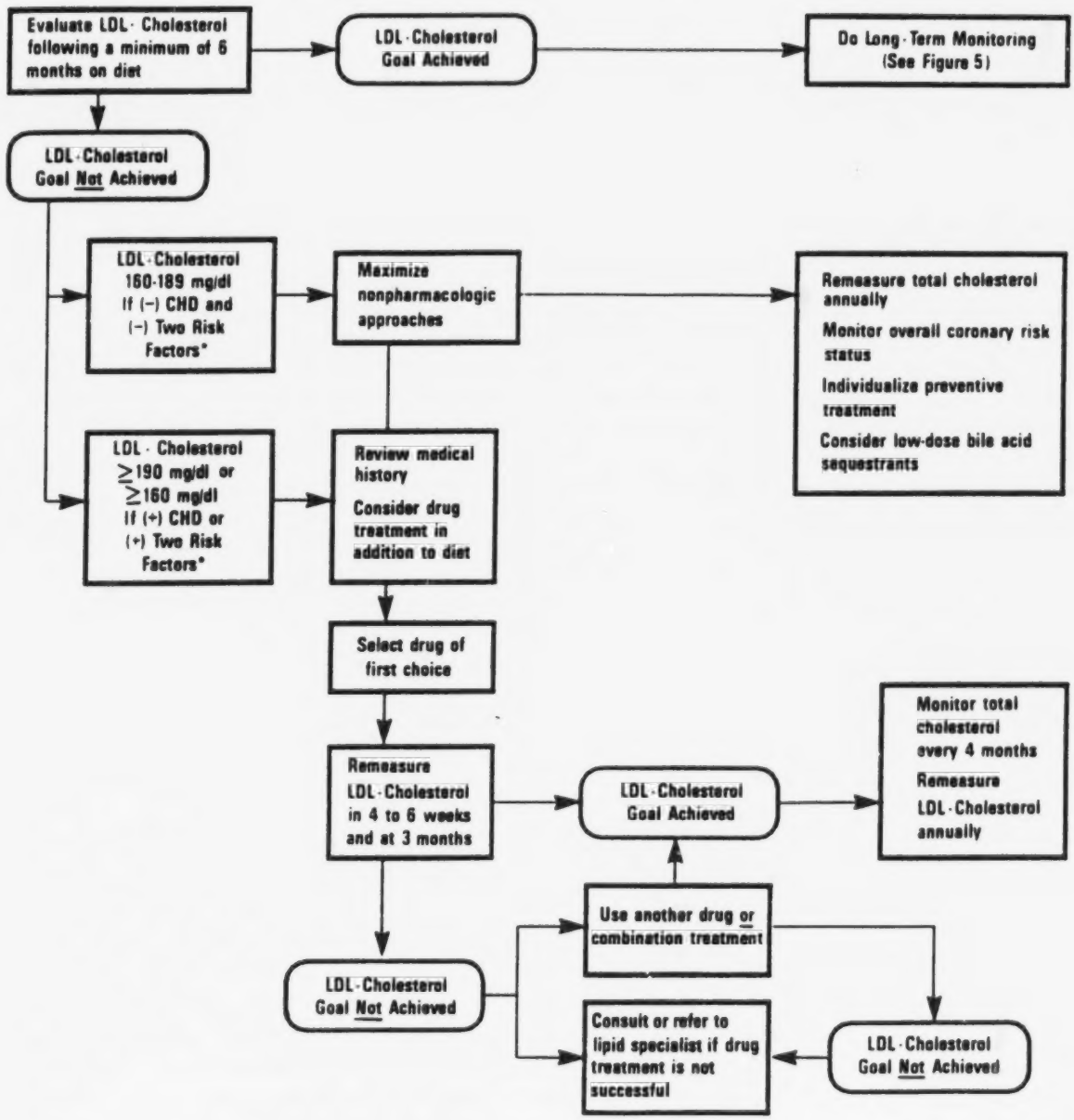
The use of the bile acid sequestrants and nicotinic acid requires frequent observation or contact with the patient during the early stage of treatment. Clinic visits and/or telephone contact is usually indicated at least at monthly intervals for 3-4 months. Lovastatin requires continuing liver function and lens evaluation. Thus, there is a need for judgment regarding the frequency of visits and observation during the early phases of drug therapy. When the final drug regimen has been established, follow-up visits should continue at 4-month intervals to promote adherence. Many of the routine patient contacts may not need direct physician

ERRATA

Page 60. Please substitute the following figure for Figure 6:

FIGURE

6 — *Drug Treatment*


Evaluate LDL-Cholesterol following a minimum of 6 months on diet
LDL-Cholesterol Goal Achieved
Do Long-Term Monitoring (See Figure 5)
LDL-Cholesterol Goal Not Achieved
LDL-Cholesterol 160-189 mg/dl If (-) CHD and (-) Two Risk Factors*
Maximize nonpharmacologic approaches
Remeasure total cholesterol annually
Monitor overall coronary risk status
Individualize preventive treatment
Consider low-dose bile acid sequestrants
LDL-Cholesterol ≥190 mg/dl or ≥160 mg/dl If (+) CHD or (+) Two Risk Factors*
Review medical history
Consider drug treatment in addition to diet
Select drug of first choice
Remeasure LDL-Cholesterol in 4 to 6 weeks and at 3 months
LDL-Cholesterol Goal Achieved
Monitor total cholesterol every 4 months
Remeasure LDL-Cholesterol annually
Use another drug or combination treatment
LDL-Cholesterol Goal Not Achieved
Consult or refer to lipid specialist if drug treatment is not successful
LDL-Cholesterol Goal Not Achieved

*One of which can be male sex.

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involvement but may be handled instead by physician's assistants, nurses, pharmacists, or dietitians.

If the patient has had at least a 15% decrease in LDL-cholesterol and is tolerating the drug but has not achieved the minimum target goal for LDL-cholesterol, consideration should be given to adding another drug as discussed in the Combined Drug Treatment section. If the patient has not had a 15% decrease in LDL-cholesterol or is not tolerating the drug, the physician should either switch to another drug or proceed to combination therapy, if necessary. Consultation with a lipid specialist may be useful in the management of patients with persistently high LDL-cholesterol levels despite dietary and drug therapy.

D. *Adherence to Drug Therapy*

1. *General Comments.*

Drug therapy is likely to continue for a lifetime or for a very prolonged period of time. Hence, the patient must be well informed about the goals of drug treatment and the side effects of medication. The need for a long-term commitment must be emphasized. When dealing with the selection of bile acid sequestrants versus newer, "easier" drugs, safety must be emphasized. It is important to start with small doses of the drugs, especially when using sequestrants and nicotinic acid. The patient must have time to adapt to the drug regimen, and any difficulties must be remedied before proceeding to higher doses. Health professionals who are already involved in patient education would be a logical source of help for the patient who is having problems with side effects. The initial experience with a regimen is likely to predict long-term adherence.

The frequency of medication intake and its impact on lifestyle must be frankly discussed. The planned regimen should attempt to minimize changes in daily lifestyle. Reinforcement of adherence by periodic laboratory monitoring and reassurance is essential. There is also a need for patience, an adequate amount of time, and understanding on the part of the health professional. It must be emphasized to patients that the ultimate responsibility for management is theirs, and communication with the appropriate health professional is essential when problems arise. The importance of diet in addition to drugs must continue to be emphasized. Some practical suggestions concerning adherence are summarized in Appendix IV.

2. *Patient Counseling/Assessment of Adherence.*

The management of a risk factor like elevated serum cholesterol is multifactorial and in the ideal treatment setting would call on the expertise of a variety of professionals. Time and resources dictate a more prudent approach. Drug therapy for many patients can be successfully managed by the physician in his or her office along with the assistance of an office health professional who has skill and experience in teaching patients and some understanding of the side effects of drugs and approaches to their management. This person will generally be a nurse, or a

nursing or physician's assistant. The community pharmacist is also a valuable resource for patient education. Additional educational efforts are usually required to ensure the successful utilization of the bile acid sequestrants and nicotinic acid, as compared to the other cholesterol-lowering drugs. There should be regular communication with the supervising physician, but many other health professionals can effectively educate the patient. A sensitive, caring individual who routinely sees the patient (constant caretaker model) and develops the patient's trust is often an important component of an effective adherence counseling program.

It is important that community health care providers utilize appropriate specialist consultation. Lipid specialists are available in most large metropolitan areas. Of major importance is the maintenance of continuing education in the cholesterol area, where knowledge is rapidly growing. Furthermore, consultation on an ongoing basis may be sought so that more difficult cases or situations can be reviewed and consultation obtained for planning treatment. If the target treatment goals for LDL-cholesterol are not achieved or if the patient is having considerable problems with side effects of medication, referral to a specialist in lipid disorders may be indicated. This is especially important if the patient has definite CHD, a genetic disorder with severe hypercholesterolemia, or other major risk factors. It is difficult to provide the best care possible through the use of a multidisciplinary team and also control the cost of treatment to the patient. Minimizing the number of office visits, limiting the number of direct care providers, and using the least costly provider with the broadest skills for routine care will help. Maximizing the response to dietary therapy will minimize the need for costly drug therapy. The use of standardized teaching materials that can be adapted to individual needs, and inexpensive followup between office visits (e.g., telephone or postcard exchanges) may help patients successfully follow a regimen that has been tailored to their circumstances and that has every likelihood of effectively lowering their elevated cholesterol levels.

¶¶ Additional Note: The following statement was prepared by the Steering Committee of the Cholesterol Adult Treatment Panel (Drs. Goodman, Cleeman, Brown, Grundy, Hulley, Hunninghake, and Rifkind) six weeks following the final approval of the report by the National Cholesterol Education Program Coordinating Committee:

Subsequent to the formal endorsement of this report by the National Cholesterol Education Program Coordinating Committee, the results of the Helsinki Heart Study were reported (Frick, M. H. et al. N Engl J Med 1987; 317:1237-45). This randomized, double-blind, five-year trial tested the clinical efficacy and safety of gemfibrozil, 600 mg twice daily, vs. placebo in 4,081 asymptomatic middle-aged men with elevated blood cholesterol levels. Gemfibrozil moderately reduced the serum levels of total and LDL-cholesterol, and also reduced triglycerides and increased HDL-cholesterol levels. The incidence of CHD was reduced by 34% in the drug-treated group ($p < 0.02$). This trial thus demonstrates the clinical efficacy and safety of gemfibrozil in reducing coronary risk in patients with high cholesterol levels. In view of these results, it would be reasonable for physicians to consider the use of gemfibrozil more readily when selecting drugs for patients with high cholesterol levels who meet the criteria for drug treatment. Gemfibrozil may be particularly useful, as an alternative to nicotinic acid, in patients with high-risk LDL-cholesterol levels who also have borderline hypertriglyceridemia (triglyceride levels 250-500 mg/dl) and low HDL-cholesterol levels. More extensive review and evaluation of the results of the Helsinki Heart Study may further clarify the place of gemfibrozil in the treatment of patients with high blood cholesterol.

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Total Cholesterol and LDL-Cholesterol Distributions in the U.S. Population by Age and Sex NHANES Data (Serum)

TABLE

I-1.— *Mean serum cholesterol levels of men, standard errors of the mean, age-adjusted values, selected percentiles, number of examined persons, and estimated population, by race and age: United States, 1976-80*

Race and age	Examined persons	Estimated population	Mean	Standard error of the mean	Percentile								
					5th	10th	15th	25th	50th	75th	85th	90th	95th
All races[1]	Number	Number in thousands	Serum cholesterol in milligrams per deciliter										
20-74 years	5,584	83,611	211	1.2	144	158	165	179	208	239	258	271	291
20-24 years	876	9,331	180	1.7	129	138	145	155	178	202	215	227	246
25-34 years	1,067	15,895	199	1.5	141	152	159	172	194	220	240	254	275
35-44 years	746	11,387	217	2.0	153	166	173	187	215	244	262	276	293
45-54 years	998	11,114	227	1.8	159	176	182	197	223	255	271	283	303
55-64 years	1,227	8,697	229	1.8	164	178	184	198	225	254	277	288	307
65-74 years	1,199	8,287	221	1.8	153	167	175	191	217	249	265	279	301
White													
20-74 years	4,883	55,808	211	1.2	145	157	166	179	207	239	258	271	291
20-24 years	581	8,052	180	1.8	131	138	146	155	176	202	216	229	244
25-34 years	901	13,864	199	1.7	144	153	161	172	194	220	239	254	273
35-44 years	653	9,808	217	1.8	153	166	173	187	214	244	260	272	291
45-54 years	617	9,865	227	1.8	160	177	181	198	222	254	271	283	303
55-64 years	1,086	8,642	230	2.0	164	176	185	199	225	255	278	289	307
65-74 years	1,045	5,576	222	2.0	153	167	175	191	217	250	266	281	301
Black													
20-74 years	607	6,102	208	2.5	133	146	156	171	200	236	260	273	301
20-24 years	79	1,043	171	*3.7	*	128	134	149	170	193	210	211	*
25-34 years	139	1,546	198	*4.1	129	136	144	163	192	226	248	259	301
35-44 years	70	1,112	218	*8.3	*	156	168	176	202	238	275	283	*
45-54 years	62	1,044	229	*7.1	*	174	184	195	232	261	268	279	*
55-64 years	129	801	223	*4.8	157	168	172	183	218	254	271	299	312
65-74 years	128	555	217	4.2	149	163	173	183	216	244	261	277	299
Age-adjusted values:													
All races, 20-74 years	...	...	211	1.1	...	...	...	...	...	...	...	...	...
White, 20-74 years	...	...	211	1.1	...	...	...	...	...	...	...	...	...
Black, 20-74 years	...	...	209	2.5	...	...	...	...	...	...	...	...	...

[1]Includes data for races not shown separately.

Source: National Center for Health Statistics; Fulwood, R.; Kalsbeck, W.; Rifkind, B.; Russell-Briefel, R.; Muesing, R.; LaRosa, J.; Lippel, K. Total serum cholesterol levels of adults 20-74 years of age: United States, 1976-80. Vital and Health Statistics, Ser. II, No. 236. DHHS Pub. No. (PHS) 86-1686. Public Health Service. Washington, DC: US Government Printing Office, May 1986.

TABLE

I-2.— *Mean serum cholesterol levels of women, standard errors of the mean, age-adjusted values, selected percentiles, number of examined persons, and estimated population, by race and age: United States, 1976-80*

Race and age	Examined persons	Estimated population	Mean	Standard error of the mean	Percentile								
					5th	10th	15th	25th	50th	75th	85th	90th	95th
All races[1]	Number	Number in thousands	Serum cholesterol in milligrams per deciliter										
20-74 years	6,268	69,984	215	1.2	143	150	156	179	213	246	266	282	305
20-24 years	738	9,894	184	1.9	132	140	145	157	180	204	216	230	250
25-34 years	1,170	16,858	192	1.4	135	145	154	164	188	215	233	243	263
35-44 years	844	12,284	207	1.8	147	158	164	177	202	231	248	260	276
45-54 years	783	11,918	232	2.2	164	176	186	198	228	257	276	290	306
55-64 years	1,328	10,743	249	2.0	180	193	203	215	242	277	298	314	336
65-74 years	1,416	8,198	248	1.6	173	189	198	214	241	274	295	309	327
White													
20-74 years	5,418	60,785	216	1.3	143	150	156	179	210	246	267	282	305
20-24 years	624	8,408	184	2.1	133	140	147	159	181	204	215	230	249
25-34 years	1,000	14,494	192	1.5	135	145	153	164	188	215	235	244	261
35-44 years	725	10,584	207	1.9	147	157	164	177	203	231	248	250	277
45-54 years	647	10,369	232	2.6	166	179	188	199	228	257	274	290	308
55-64 years	1,176	9,601	249	1.7	180	193	203	215	244	277	298	312	330
65-74 years	1,245	7,329	246	1.7	174	190	199	214	242	275	296	309	328
Black													
20-74 years	729	7,579	212	3.1	140	154	166	176	205	237	263	279	308
20-24 years	94	1,304	185	*4.9	*	138	144	158	178	204	220	237	*
25-34 years	145	1,953	191	*4.1	129	144	156	167	190	212	226	235	267
35-44 years	103	1,415	206	*4.5	143	158	170	175	194	233	254	274	279
45-54 years	100	1,215	230	*7.2	150	172	181	200	226	263	277	291	306
55-64 years	135	959	251	*8.0	178	185	198	211	233	280	318	336	345
65-74 years	152	733	243	4.2	173	189	198	211	237	269	290	308	323
Age-adjusted values:													
All races, 20-74 years	...	...	215	1.2	...	...	...	...	...	...	...	...	...
White, 20-74 years	...	...	215	1.2	...	...	...	...	...	...	...	...	...
Black, 20-74 years	...	...	214	2.7	...	...	...	...	...	...	...		

[1]Includes data for races not shown separately.

Source: National Center for Health Statistics; Fulwood, R.; Kalsbeck, W.; Rifkind, B.; Russell-Briefel, R.; Muesing, R.; LaRosa, J.; Lippel, K. Total serum cholesterol levels of adults 20-74 years of age: United States, 1976-80. Vital and Health Statistics, Ser. II, No. 236. DHHS Pub. No. (PHS) 86-1686. Public Health Service. Washington, DC. US Government Printing Office, May 1986.

TABLE

I-3.—*Calculated levels of serum low density lipoprotein cholesterol[1] for persons,[2] ages 20-74 years fasting 12 hours or more by sex and age: means and selected percentile: United States, 1976-80.*

Sex and age	Examined persons	Estimated Population	Mean	Standard Deviation	Percentile								
					5th	10th	15th	25th	50th	75th	85th	90th	95th
Male	Number	Number in Thousands			Serum LDL-cholesterol in milligrams per deciliter								
20-74 years	1,037	21,262	140	39	80	92	100	113	136	164	181	194	208
20-24 years	72	1,852	109	36	*	70	74	88	104	129	149	154	*
25-34 years	174	6,186	128	33	76	87	94	108	128	148	161	171	189
35-44 years	130	3,866	145	40	81	96	105	116	138	176	192	203	206
45-54 years	108	3,543	150	38	99	103	112	119	146	171	189	195	211
55-64 years	287	3,843	148	39	84	101	108	118	147	171	191	206	217
65-74 years	288	2,872	149	40	87	105	109	120	144	174	188	199	217
Female													
20-74 years	1,246	27,102	141	43	81	91	98	110	136	164	186	199	220
20-24 years	105	3,325	114	33	69	74	83	94	106	136	149	155	179
25-34 years	194	5,517	121	33	72	83	90	98	116	139	154	166	187
35-44 years	166	4,800	129	34	78	90	97	107	126	150	163	171	191
45-54 years	168	5,155	157	45	94	104	116	125	156	184	200	213	226
55-64 years	282	4,644	159	42	101	113	118	129	150	188	205	219	237
65-74 years	331	3,661	162	44	98	109	122	135	158	186	207	226	245

[1] Serum LDL-Cholesterol = Serum Total Cholesterol - HDL-Cholesterol - (Triglycerides/5). Equation from Friedewald, WT et al. Clin Chem 1972; 18:499-502. Persons with a serum triglyceride value greater than 400 mg/dl were excluded.

[2] Includes other races in addition to black and white.

* Sample size insufficient to produce statistically reliable results.

Source: National Center for Health Statistics: Division of Health Examination Statistics, unpublished data from the second National Health and Nutrition Examination Survey, 1976-80

TABLE

I-4.—Corresponding Levels of Lipids in mg/dl and mmol/L

Cholesterol		Triglycerids	
mg/dl	mmol/L	mg/dl	mmol/L
35	0.9	200	2.3
130	3.4	400	4.5
160	4.1	500	5.6
180	4.6	1,000	11.3
200	5.2		
240	6.2		

Special Patient and Population Groups

This section is provided to review for the practitioner the major forms of severe hypercholesterolemia, the problem of high plasma triglycerides, causes of reduced HDL-cholesterol, and manifestations of diabetic dyslipidemia. Its purpose is to assist the physician in management of these problems or help in identification of disorders that would be better treated by a specialist in this field. There are two reasons for referring a hyperlipidemic patient to a specialist. First, the dyslipidemia may be severe or complicated and beyond the experience of a given practitioner; and, second, the patient may require special testing that is beyond the capability of laboratories available to the physician. The latter may be particularly the case for rare or severe disorders of lipoprotein metabolism. In some instances, a precise etiologic diagnosis may be required for the correct treatment of a patient.

1. *Severe Forms of Hypercholesterolemia.*

(a) *Familial hypercholesterolemia (FH).*

This disorder is caused by a defect in the gene encoding for the LDL receptor such that the receptor is either absent or nonfunctional. One gene for the LDL receptor normally is inherited from each parent. In the heterozygous form of FH, the patient has only one normal gene for LDL receptors, and LDL-cholesterol levels are approximately doubled, to levels exceeding 200 mg/dl. Heterozygous FH occurs approximately once in 500 people, and serum total cholesterol levels usually exceed 300 mg/dl; affected patients frequently have tendon xanthomas, corneal arcus, premature CHD, and a strong family history of hypercholesterolemia. Approximately 5% of patients with myocardial infarction before 60 years of age will have heterozygous FH. Affected men often develop CHD in their 30's or 40's, or even earlier; in women with FH, CHD often occurs in the 50's and 60's. Rarely, about once per million people, individuals inherit two abnormal genes for LDL receptors and hence are homozygous for FH. Their cholesterol levels range from 600-1,000 mg/dl (15.5-25.9 mmol/L); they usually have planar and tuberous xanthomas of the hands, elbows, buttocks, and knees as well as tendon xanthomas. Severe and often fatal coronary disease frequently develops in the teens.

Patients with heterozygous FH rarely respond adequately to dietary therapy alone. Certainly the Step-Two Diet will potentiate the action of specific cholesterol-lowering drugs, and affected patients should be encouraged to modify their diets to obtain maximal cholesterol lowering. Some patients with FH respond remarkably to diet, and the potential value of diet modification should not be overlooked. However, in most patients, it is not necessary to wait for 6 months of dietary therapy before beginning drug treatment. To attain the goals of LDL lowering in patients with heterozygous FH, two drugs frequently are required. At present, the combination of a bile acid sequestrant and nicotinic acid is the most potent regimen available. Recent evidence indicates that use of HMG CoA reductase

inhibitors (e.g., lovastatin) in combination with bile acid sequestrants will reduce LDL-cholesterol levels into the normal range in many people with heterozygous FH. In homozygous FH, more drastic means are required to lower LDL levels. These patients respond poorly to drugs, including reductase inhibitors, and more radical therapies have been tried, including portacaval shunt, liver transplantation, and direct removal of LDL by a modified form of plasmapheresis.

(b) Familial combined hyperlipidemia (FCHL).

Another form of primary hypercholesterolemia occurs in some individual members of families having FCHL. In FCHL, multiple lipoprotein phenotypes can occur in a single affected family. About one-third of affected patients have increases in VLDL alone [type 4 hyperlipoproteinemia (HLP) pattern]; another third have increases in LDL alone (type 2a HLP), while most others have elevations of VLDL + LDL (type 2b HLP) or VLDL + chylomicrons (type 5 HLP). Hyperapobetalipoproteinemia [increased LDL-apolipoprotein B (apo-B) with normal LDL-cholesterol] is another lipoprotein pattern commonly found in FCHL. The diagnosis of FCHL is made by testing of first-degree relatives and by finding multiple lipoprotein phenotypes in a single family. Patients with FCHL are at increased risk for CHD regardless of their lipoprotein phenotype. FCHL occurs in about 15% of patients with CHD before 60 years of age. The underlying metabolic defect in many families appears to be an overproduction of lipoproteins by the liver, and the resulting lipoprotein phenotype depends on how rapidly these excess lipoproteins are cleared from the circulation. For example, when rates of clearance of LDL are sluggish, the patient will develop an elevation of LDL-cholesterol.

Dietary therapy can play an important role in the treatment of primary hyperlipidemia due to overproduction of lipoproteins. Patients with FCHL may be extremely sensitive to even a few pounds of excess body weight, and reduction of weight to the desirable range sometimes will lower plasma lipid levels substantially. Further improvement in the lipoprotein pattern may be achieved by instituting a program of regular physical exercise. Restriction of dietary cholesterol and saturated fatty acids may further reduce LDL-cholesterol levels. In many patients with FCHL, however, drug therapy may be required to completely or adequately control plasma levels of lipoproteins. The drug of choice for FCHL is nicotinic acid, which interferes with the excessive formation of lipoproteins. For patients with FCHL who have elevated LDL with normal triglyceride levels and who cannot tolerate nicotinic acid, a bile acid binding resin or the new drug lovastatin can be used; these latter agents alone, however, may not be sufficient in patients with a concomitant elevation of plasma triglycerides, as will be discussed below in Section 2 (Hypertriglyceridemia).

(c) Severe primary hypercholesterolemia.

About 1% of the adult population have cholesterol levels that are persistently over 300 mg/dl. A portion of individuals in this group will have heterozygous FH that is unrecognized, either because of a lack of tendon xanthomas or unavailability of

first-degree relatives for testing. In others, a definite monogenic inheritance of elevated LDL-cholesterol cannot be demonstrated, and hence the term "polygenic" hypercholesterolemia has been used. While people in this category may merely represent the upper end of the spectrum of the population distribution of plasma cholesterol, they deserve special attention because of the severity of their hypercholesterolemia and their greatly heightened risk for CHD. Furthermore, patients of this category often have a diet-resistant form of hypercholesterolemia and must be managed with drugs. When it becomes obvious that patients of this type will not reach the goals of LDL lowering by dietary therapy alone, drug treatment can be instituted. Some patients may require a combination of drugs, as described above for FH, but others may respond adequately to a first-choice drug, or the new drug lovastatin.

(d) Familial dysbetalipoproteinemia (type 3 hyperlipoproteinemia).

This is a relatively uncommon condition that occurs roughly in about 1 in 5,000 persons in the United States, in which catabolism of remnants of VLDL and chylomicrons is delayed. The normal apo E phenotype is E_3, while the phenotype of type 3 HLP is E_2. The basic abnormality lies in the primary structure of apolipoprotein E (apo E). The structural alteration of apo E prevents the normal binding of VLDL remnants to LDL receptors on liver and other cells. The accumulation of modified VLDL remnants (called beta-VLDL) accounts for the term *dysbetalipoproteinemia*. The VLDL in these patients have beta mobility on lipoprotein electrophoresis rather than the normal prebeta mobility. The disorder should be suspected when triglyceride levels are somewhat higher than cholesterol levels in the presence of striking cholesterol elevation. Patients with dysbetalipoproteinemia have an increased risk of premature CHD and peripheral vascular disease; they commonly are obese, glucose intolerant, hyperuricemic, and have tuboeruptive and palmar xanthomas. Despite hypercholesterolemia, the LDL-cholesterol rarely is increased in dysbetalipoproteinemia, and the increase in cholesterol levels occurs in the VLDL fraction; however, when LDL levels are calculated by equation, there will be an apparent increase in LDL-cholesterol. For this reason, in a patient with an elevation in both triglycerides and cholesterol, the physician should be alert to the possibility of dysbetalipoproteinemia, and appropriate testing should be done—including referral to a specialist if necessary.

If a patient with type 3 HLP is overweight, caloric restriction frequently reduces cholesterol levels to normal. If diabetes mellitus contributes to the hyperlipidemia, control of hyperglycemia will often be helpful, but may not eliminate the need to use specific lipid-lowering drugs. Clinical experience has shown that restriction of excess total calories, saturated fatty acids, and cholesterol in the diet will significantly reduce total cholesterol levels in many patients with familial dysbetalipoproteinemia. When hyperlipidemia persists in spite of maximal dietary therapy, drug therapy should be instituted. Nicotinic acid is the drug of choice for this disorder. The fibric acids (gemfibrozil and clofibrate) also have proven highly effective for reducing both cholesterol and triglycerides in dysbetalipoproteinemia.

The bile acid sequestrants should not be used as single drug therapy in patients with type 3 HLP because these drugs will increase the cholesterol and triglyceride levels.

2. *Hypertriglyceridemia.*

(a) Definition.

The National Institutes of Health Consensus Development Conference on Treatment of Hypertriglyceridemia defined definite hypertriglyceridemia as a fasting plasma triglyceride level exceeding 500 mg/dl (22). This conference classified triglyceride levels in the range of 250-500 mg/dl as "borderline hypertriglyceridemia." The NIH Consensus Panel concluded: "There is little evidence that triglyceride levels below 250 mg/dl in the presence of normal cholesterol levels predict an increased risk of any disease. These levels (generally) can be considered normal." The present report generally follows the recommendations of this NIH Consensus Panel.

For most patients, triglyceride levels in the range of 250-750 mg/dl (2.8-8.5 mmol/L) result mainly from increases in VLDL (type 4 HLP). When triglyceride levels are higher, the patient usually has elevations of both VLDL and chylomicrons (type 5 HLP). Very rarely patients have a congenital absence of lipoprotein lipase and have severe chylomicronemia (type 1 HLP).

(b) Plasma triglycerides and disease.

The relationship between plasma triglyceride levels and cardiovascular disease is controversial. Although plasma triglyceride levels are positively associated with increased risk for cardiovascular disease in most population studies, in most they were not independently predictive for CHD after statistical adjustment for closely associated attributes such as total cholesterol, HDL-cholesterol, hypertension, cigarette smoking, and obesity. In the Framingham Heart Study, however, the plasma triglyceride level was found to be an independent predictor of CHD in women (21). Even so, the plasma triglyceride level, rather than being a direct cause of atherosclerotic disease, probably reflects the presence of certain atherogenic lipoproteins. Certainly, many disease entities that elevate triglyceride levels, such as diabetes mellitus, nephrotic syndrome, and chronic renal disease, carry an increase in risk for CHD. Furthermore, some patients with FCHL have borderline hypertriglyceridemia and normal serum cholesterol levels and yet are still at increased risk for CHD. In these situations, the high triglyceride level may be a clue to the presence of other lipoprotein abnormalities that are more directly associated with CHD, such as low HDL-cholesterol, low apoprotein A-1, elevated apoprotein B, or atherogenic remnant lipoproteins that have not been well defined. When assessing the risk for CHD in a patient with borderline hypertriglyceridemia, reliance should be placed first on the standard cholesterol risk factors, viz., total cholesterol, LDL-cholesterol, and HDL-cholesterol. Beyond these, additional factors suggesting increased coronary risk in patients with hypertriglyceridemia are the presence in first-degree relatives of hypercholesterolemia, premature CHD, and, if the test is available, increased plasma levels of apo B.

A link between plasma triglycerides and disease is most clearly evident in patients who have severe hypertriglyceridemia with chylomicronemia and eruptive xanthomata; these patients are prone to abdominal pain and/or pancreatitis, the latter occasionally being fatal. Severe elevations of chylomicrons directly induce pancreatitis, and it can be prevented by triglyceride reduction.

(c) Candidates for specific therapy.

Much of *borderline hypertriglyceridemia* seen in clinical practice is due to various exogenous or secondary factors raising the plasma triglyceride level. The most common is obesity. Others include excessive intake of alcohol, diabetes mellitus, hypothyroidism, chronic renal disease—uremia, nephrotic syndrome, maintenance dialysis, renal transplantation—liver disease, and, rarely, dysproteinemias. There are also a number of drugs that raise lipid levels as a significant side effect. These may primarily act on VLDL and raise triglyceride levels, rather than act on LDL. These include several drugs used to lower blood pressure (including the thiazide diuretics and beta-adrenergic blocking agents), estrogenic hormones (including oral contraceptives), and retinoids. The clinician evaluating a patient's blood lipid levels should be aware of this phenomenon.

Borderline hypertriglyceridemia also can be one manifestation of certain familial hyperlipidemias. One such entity is familial combined hyperlipidemia (FCHL), described above. Patients with FCHL have an increased risk for CHD regardless of their lipoprotein phenotype, including isolated borderline elevated plasma triglycerides. Because of heightened coronary risk, patients with FCHL deserve treatment with diet first, and if necessary, with drugs. Furthermore, any patient with primary borderline hypertriglyceridemia who already has clinical manifestations of premature cardiovascular disease can be treated as if he or she has FCHL.

Borderline hypertriglyceridemia likewise can be a manifestation of another familial disorder called familial hypertriglyceridemia (FHTG). Most patients with FHTG appear to have a mild defect in lipolysis of triglyceride-rich lipoproteins combined with an overproduction of VLDL-triglycerides. The VLDL are enriched in triglycerides, but the number of VLDL particles entering plasma apparently is not increased, and consequently LDL-cholesterol concentrations are not increased. Patients with FHTG seem to be at lesser risk for CHD than those with FCHL. In FHTG, there generally is a lack of elevated blood cholesterol, either in the patient or other family members, and affected members are less likely to have premature CHD. Caloric restriction and increased exercise can be strongly recommended for obese patients with FHTG, but drug therapy is generally not appropriate for this condition alone.

The NIH Consensus Panel based its definition of *definite hypertriglyceridemia* on the following considerations: "Fasting plasma triglyceride levels above 1,000 mg/dl carry a significant risk of pancreatitis. Based on this risk coupled with the large intraindividual variation in repeated triglyceride measurements, a triglyceride level greater than 500 mg/dl is considered to be abnormal, and warrants the label

hypertriglyceridemia." Patients with definite hypertriglyceridemia also can have primary or secondary disorders of triglyceride metabolism, and not infrequently these two categories are present in a single patient.

Very high triglyceride levels (>1,000 mg/dl) are due in large part to accumulation of chylomicrons. Rare genetic causes of severe chylomicronemia are congenital absence of lipoprotein lipase or apolipoprotein C-II, the latter being required for activation of lipoprotein lipase; these conditions usually become manifest first in childhood. Severe hypertriglyceridemia in adults sometimes is due to a primary disease (FHTG or FCHL) plus exacerbating secondary factors such as obesity, poorly controlled diabetes mellitus, excess use of alcohol, or drugs (e.g., corticosteroids, estrogens, or beta-adrenergic blocking agents). In such patients, both children and adults, immediate and long-term reduction of plasma triglycerides is mandatory to prevent recurrent abdominal pain and pancreatitis.

(d) Dietary therapy in patients with hypertriglyceridemia.

Changes in lifestyle (control of weight, increased physical activity, restriction of alcohol, and, in some cases, restriction of dietary fat) are the primary modes of therapy for hypertriglyceridemia. Patients with triglyceride levels in excess of 500 mg/dl, like those with high cholesterol levels, may benefit from counseling with a registered dietitian. Specific dietary approaches to the major forms of hypertriglyceridemia can be considered briefly.

For patients with severe hypertriglyceridemia and chylomicronemia, a very-low-fat diet (10-20% of total caloric intake as fat) should be instituted to prevent pancreatitis. The need to maintain this diet at all times must be emphasized. Some chylomicronemic patients are extremely sensitive to dietary fat and can develop pancreatitis from a single high-fat meal. In some patients, repeated bouts of pancreatitis will occur despite all attempts at dietary control, and drug therapy will be required.

In patients with borderline hypertriglyceridemia, emphasis should be on weight reduction and increasing physical activity. In this condition, very-low-fat, high-carbohydrate diets are not required and may actually accentuate hypertriglyceridemia. Therefore, it is not advisable to go beyond the Step-One Diet in reduction of fat intake. With secondary hypertriglyceridemias, one should treat the underlying disorder, but sometimes treatment can be facilitated by modifying the diet, usually by weight reduction and alcohol restriction.

(e) Drug therapy in patients with hypertriglyceridemia.

The NIH Consensus Panel reported: "Drug therapy in hypertriglyceridemia should take a second place to modification of the diet. Drugs nevertheless may be required to avoid abdominal pain and pancreatitis in the presence of chylomicronemia. They also can be used to produce regression of xanthomata in patients of this kind or in those with familial dysbetalipoproteinemia. Drugs also may be employed in the

attempt to retard atherogenesis in patients with genetic hyperlipidemias, such as FCHL or familial dysbetalipoproteinemia." The current report supports these recommendations.

For patients with marked hypertriglyceridemia, who do not respond adequately to modification of the diet, drug therapy can be justified to reduce the risk for acute pancreatitis. Nicotinic acid is the drug of choice here, but if this drug is not tolerated, many patients will respond sufficiently to a fibric acid (gemfibrozil or clofibrate) to eliminate the risk for pancreatitis. Bile acid binding resins are not appropriate for patients with hypertriglyceridemia.

The role of drugs in the treatment of borderline hypertriglyceridemia is controversial. Most patients in this category will have diet-induced hypertriglyceridemia and thus are not candidates for drug therapy. If a patient has the characteristics of FHTG, which does not carry an increased risk of CHD, the use of drugs is not warranted. On the other hand, if a hypertriglyceridemic patient has been shown to have FCHL, which imparts increased risk, lipid-lowering drug therapy is appropriate. Nicotinic acid is the drug of choice for FCHL, because it curtails the overproduction of lipoproteins that is characteristic of this disorder. An alternative approach is to reduce triglyceride levels with a fibric acid and to simultaneously lower LDL concentrations with either a bile acid binding resin or lovastatin. If a diagnosis of FCHL cannot be made by family testing, factors that suggest the presence of this disorder in individual patients include the presence of CHD, high blood cholesterol, high-risk LDL-cholesterol, reduced HDL-cholesterol, and a family history of CHD. Opinion is divided whether such patients are candidates for drug therapy. A conservative approach is to restrict the use of drugs to patients with high levels of total cholesterol and LDL-cholesterol. A more aggressive approach is to treat elevated triglycerides, high VLDL-cholesterol levels, and reduced HDL-cholesterol concentrations with nicotinic acid or a fibric acid; however, it must be emphasized that this latter approach has not been proven by controlled clinical trials to reduce the risk for CHD.

3. *Reduced HDL-Cholesterol.*

In this document, a reduced serum level of HDL-cholesterol is defined as a concentration below 35 mg/dl (0.9 mmol/L). A reduced HDL-cholesterol level imparts an increased risk for CHD, and hence is classified as a major risk factor. As indicated in the text, the HDL-cholesterol concentration should be measured in all patients with high blood cholesterol levels, and in persons with borderline-high blood cholesterol levels and a high risk status (definite CHD or two other major risk factors, one of which can be male sex). The presence of a reduced serum HDL-cholesterol is one factor favoring the use of drugs to treat high LDL-cholesterol concentrations.

The major causes of a reduced serum HDL-cholesterol level are listed in Appendix Table II-1. Heavy cigarette smoking is a documented cause, and, in smokers, the

reduction in HDL-cholesterol appears to be made worse by concomitant heavy use of coffee. Obesity is a major cause of reduced concentrations of HDL, and a closely related cause is a lack of physical activity. White men, but not necessarily black men, have lower HDL levels than women. Anabolic steroids and progestational agents decrease the HDL-cholesterol concentration. Among other drugs, the beta-adrenergic blocking agents most consistently reduce the HDL level. Hypertriglyceridemia, even in mild forms, is frequently associated with significantly decreased levels of HDL-cholesterol, and, in some patients, elevated LDL-cholesterol is accompanied by a reduced concentration of HDL. Finally, poorly understood genetic factors account for a portion of cases of reduced HDL-cholesterol.

Although there have been no clinical trials demonstrating the benefit of raising HDL-cholesterol, the connection between reduced HDL-cholesterol and CHD risk justifies the attempt to raise HDL levels, particularly when this can be accomplished by hygienic means. Appropriate advice is to stop use of cigarettes in smokers, reduce body weight in the obese, increase exercise in the sedentary, and avoid use of anabolic steroids in athletes. For patients with a reduced HDL-cholesterol, avoiding the use of beta-blockers for treatment of hypertension may be prudent, although these drugs may be required for patients with definite CHD. One result of treating hyperlipidemia is that HDL-cholesterol concentrations frequently increase, which may be of added benefit.

4. *Diabetic Dyslipidemia.*

Diabetes mellitus is a major risk factor for CHD, and, in accord with the recommendations of this report, the minimal goal of LDL lowering in diabetic men is to achieve a reduction of LDL-cholesterol to less than 130 mg/dl. For diabetic women, the minimal LDL-cholesterol goal is <160 mg/dl in the absence of CHD or another risk factor, or <130 mg/dl if definite CHD or another risk factor is present. Abnormal plasma lipid and lipoprotein levels frequently are seen in diabetics. Careful control of plasma glucose will reduce LDL levels, and HDL-cholesterol concentrations frequently will rise. Control of hyperglycemia is the key to improving the lipoprotein pattern in diabetics. The dietary therapy outlined for other high-risk patients with elevated LDL levels is recommended by many authorities for diabetic patients. Other investigators believe that intake of carbohydrates should not exceed 40-45% of total calories; if this latter approach is accepted, the intake of saturated fatty acids and cholesterol still should be curtailed, as recommended for other patients at high risk.

The most obvious lipoprotein abnormality in patients with noninsulin dependent diabetes mellitus (NIDDM) is hypertriglyceridemia. In occasional, poorly controlled diabetics, severe chylomicronemia can develop, and risk for acute pancreatitis is high. In these unusual patients, intake of fat must be severely restricted, at least temporarily, to prevent further synthesis of chylomicrons; furthermore, adequate doses of insulin are needed to restore normal activity of lipoprotein lipase. The

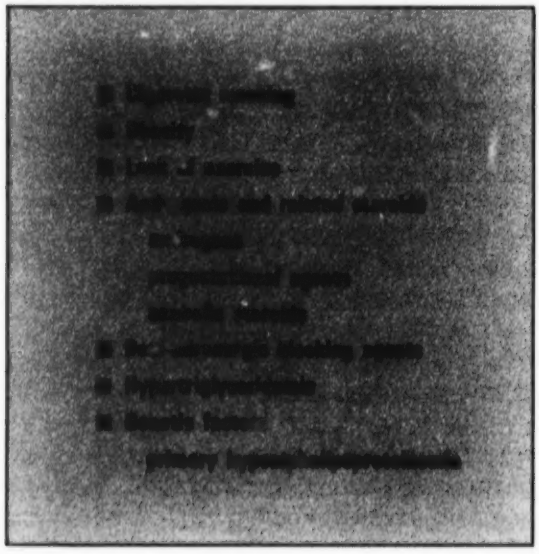
milder forms of hypertriglyceridemia that occur in many diabetics are the result of poor control of hyperglycemia, and their triglycerides can be reduced by improved glucose control. If hypertriglyceridemia persists despite good control of plasma glucose levels, the patient may have an underlying familial form of hyperlipidemia.

5. *Pregnant Women with Preexisting Lipid Disorders.*

Generally, the dietary therapy previously prescribed for the lipid disorder should be continued during pregnancy. If dietary therapy is very restrictive, careful consideration should be given to assuring adequate nutrient intake. Drug therapy

TABLE

II-1.—*Major Causes of Reduced Serum HDL-Cholesterol*



should be discontinued during pregnancy, since the effect of lipid-lowering drugs on the fetus has not been carefully studied. Women with a prior history of hypertriglyceridemia should be monitored carefully; triglyceride levels above 1,000 mg/dl are associated with an increased risk of pancreatitis. Consultation with a lipid specialist may be indicated for patients with severe forms of hyperlipidemia.

Intensive Dietary Instruction and Behavior Modification

In a majority of patients with high-risk LDL-cholesterol levels, the Step-One Diet should prove sufficient to reach the goals of dietary therapy. For most patients, it should not be necessary to refer to a dietitian. A dietitian can, however, be helpful even for these patients. For a minority of patients, more intensive dietary therapy will be needed, and referral to a registered dietitian will be important in order to effectively implement therapy. The dietitian can play a vital role in education of the patient in the process of dietary change, and the dietitian will be especially valuable for instruction of the patient in the Step-Two Diet. In this Appendix, the general approach to intensive dietary therapy under the supervision of a registered dietitian is outlined. The purpose of this section is to provide the physician and immediate staff with information about the techniques employed by many dietitians for institution and maintenance of intensive dietary therapy (including the Step-Two Diet). If the physician and staff are thoroughly familiar with the principles of dietary therapy, as outlined in this Appendix, this understanding will facilitate their interaction with the dietitian and will increase the chances of success in achieving the goal of therapy by diet modification alone. The usual steps employed by the dietitian are the following.

1. *Assessment of Nutritional Status and Eating Habits.*

A thorough assessment of the patient's dietary history and current eating habits is useful in implementation of dietary change. This assessment will include the recording of the patient's current weight and weights at significant ages. The dietitian will estimate percentage of desirable body weight, and in some cases the percentage of body fat, to determine whether the patient needs to lose weight. A detailed description of current eating habits will be obtained. Examples of the types of information that are obtained include:

a) What times of the day does the patient usually eat?

b) Are some meals routinely skipped?

c) At what time does the patient eat his/her largest meal?

d) Where are meals typically prepared (e.g. in a restaurant, work cafeteria, fast-food restaurant, deli, at home, or in the homes of others)?

e) Are meals eaten at home prepared from packaged foods or fresh from the market?

f) Which are favorite foods and what foods are disliked?

g) What foods will be most difficult to increase or decrease?

Furthermore, the dietitian will attempt to assess the patient's general state of knowledge of nutrition and its relation to high cholesterol levels, educational level, motivation, attitudes toward diet, and structure of social support.

2. *Initial Instructions for Diet Modification.*

The dietitian will describe for the patient an overall plan for diet modification. The connection between dietary habits and blood cholesterol level will be emphasized, and particular emphasis will be given to reducing the consumption of saturated fatty acids and cholesterol, and to reducing excess body weight. The dietitian may review the contents of Table 5 with the patient and will give particular attention to foods that are unusually rich in saturated fatty acids and cholesterol. A few individuals may be taught to compute a daily record of food intake that delineates specific foods, where they are prepared, and their quantity. To learn to record quantities of different foods will require specific instruction for using measuring cups, spoons, and a food scale. The dietitian may feel that certain patients will benefit by keeping a food record for about three days as an educational exercise.

In this initial instructional process, the dietitian likely will review the patient's daily routine both during the week and on weekends, and will assist the patient in identifying lifestyle factors that might interfere with adherence. The patient will be urged to actively participate in discussion and may be given the option of evaluating several eating plans before deciding on a final diet plan. It will be pointed out to the patient that he/she may find certain foods to be unappealing at first, but over a period of time, new preferences in taste will develop.

Particular attention will be given to the sources of fat in the diet, especially fat that is "hidden" in foods such as bakery goods, cheeses, and processed meats. Suggestions will be made on how to select appropriate snack foods and prepared foods. The patient may be taught the principle of "controlled cheating," i.e., how to plan and adjust for occasional episodes off the diet without becoming discouraged and discontinuing the diet altogether. Instruction will be given on how to change the type of milk used, how to reduce meat portion size, how to substitute egg whites for whole eggs in baking, and how to use margarines and oils in the place of fats rich in saturated fatty acids. The dietitian probably will attempt to involve other individuals of significance (e.g. parents, spouse, and children) in dietary instructions.

3. *Institution of Fat-Modified Diets.*

Patients usually are started on a diet that corresponds as closely as possible to their normal eating habits. For example, if the patient always skips breakfast, he/she will not be requested to eat breakfast at the outset. If the patient always eats lunch in the cafeteria at work, he/she will be taught to make reasonable food choices rather than starting to bring lunch from home. Specific goals for eating habits will be set to allow progress toward the attainment of the composition of the Step-One Diet. Only after this first step has been attained will the dietitian attempt to progress to the Step-Two Diet.

Although the objective of the Step-One Diet is less than 10% of calories as saturated fatty acids, it usually is difficult for the average person to estimate whether the

target is being met. A realistic approach will provide specific recommendations about diet change, such as reducing meat portion size to four ounces, or substituting a tuna sandwich for a cheese sandwich two days a week. It usually is necessary to implement the specific goals in a graduated fashion, rather than all at once. This will prevent the patient from being overwhelmed, will allow him/her sufficient time for adjustment, and will engender a feeling of success and not failure. Some patients will be asked to self-monitor eating behaviors related to their eating-habit goals on a regular basis during the initiation phase. The dietitian may need to review these records periodically to detect problem areas. Finally, a schedule for follow-up visits with the dietitian often is employed to ensure adoption of and adherence to the new diet.

4. *Strategy for Behavior Modification.*

Involvement of the patient in developing appropriate behavior strategies is crucial for successful dietary change and long-term adherence to the recommended diet. For the obese patient, techniques of behavior modification have been moderately successful for achieving weight reduction, and they may be instituted for overweight patients. Further, the dietitian may modify these techniques to train patients to alter the diet composition. These techniques focus on unconscious eating habits, compulsive behavior, binge eating, lack of resistance to social pressures for eating cholesterol-raising foods, use of eating to relieve anxiety and depression, and lack of will power or self-control. The dietitian can explore all of these areas with the patient and guide him/her in overcoming these eating problems. Patients will be given the opportunity to "talk through" their eating problems and to "brainstorm" new ways to improve their eating behaviors.

5. *Monitoring and Reinforcement.*

Progress in achieving the specified dietary goals will be monitored by both the patient and the diet counselor. It is helpful for the physician to provide information on response in cholesterol levels as a guide to success in diet modification. Self-monitoring tools that are designed to meet the needs of the patient may be utilized. For example, three-day food records often are an effective monitoring tool. These records provide an estimate of adherence and can help to identify any real or potential problems. These records can also enable the patient to become more aware of the diet and related behaviors, assist in analysis of progress in dietary change, and provide reinforcement of new behaviors.

A schedule of regular follow-up visits is helpful to achieve adherence to the diet. There is a tendency for adherence to drift downward with time, and this often can be avoided by periodic visits with the dietitian. It will be especially important to give supportive followup and assistance during periods of life change or stress (e.g. marriage or divorce, loss of loved ones, job change); renewed self-monitoring during these periods may be especially helpful. Occasional meetings with other family members can help to reinforce adherence to diet modification. A constant review of

the basics will be needed to offset distortions of information resulting from misunderstandings or erroneous messages picked up from the media or other sources.

Individuals are increasingly making use of personal computers for activities at home. Software programs are now available, or will become available, for analyzing food records, for providing nutrient analysis, and for support of changes in eating patterns. These programs are available for both the lay public and for professionals at several levels of complexity. Their use for modification of the diet for individuals seems to hold great potential.

6. *Role of the Patient and Family in Dietary Therapy.*

Although intakes of saturated fatty acids and cholesterol have declined in the United States, most of our population continues to consume a diet that contributes to undesirably high cholesterol levels. The current social environment often does not provide easy access to appropriate food choices nor does it sufficiently reinforce diet modification. It is thus helpful to incorporate a social support element in nutrition education and dietary counseling. Inclusion of family and spouses in intervention sessions will significantly increase the chances of success of dietary strategies to lower cholesterol. Worksite and group strategies may be particularly successful when they integrate dietary change into the social context. New interactive methods have advantages over traditional didactic methods for providing information and reinforcement.

Practical Suggestions to Improve Drug Adherence

1. *Pre-Initiation Assessment.*

In addition to selection of a drug based on its efficacy, an attempt should be made to select a drug that the patient is likely to tolerate. The patient should participate in this discussion and can be given the option of evaluating several drugs before deciding upon the final treatment plan. A few examples of the type of preliminary deliberation might include:

- Sequestrants: good choice for young, motivated, and safety-conscious individuals. May not be a good choice for the patient who has significant constipation, existing hemorrhoids, recurrent symptoms of peptic ulcer or hiatus hernia; has a history of taking multiple drugs; or travels extensively.
- Nicotinic acid: good choice where cost is a major consideration, a tablet is preferred, or long-term effects on CHD or safety are desired. The drug may not be tolerated in the postmenopausal woman with flushing, or in the patient with angina pectoris or extensive coronary disease.
- Lovastatin: good choice for the patient receiving multiple medications, with extensive disease, or severe forms of hypercholesteremia. The patient may have concerns about the lack of long-term safety information.

There are no absolute predictors of adherence, but one should be prepared to offer special assistance to patients with conditions frequently associated with reduced adherence. These include:

- Current life changes, e.g., marital status change, job or housing change, and so on.
- Current or past history of psychological distress.
- Smokers.
- Lack of social support.
- Erratic or irregular schedules.
- Recurring physiological complaints, particulary those that might be exacerbated by any side effects of the medication.

2. *Pre-Initiation Education. (This is particularly important with the bile acid sequestrants and nicotinic acid.)*

- Sequestrants: demonstrate preparation of medication. Discuss how volume of fluid may affect palatability and large volumes may increase the sense of fullness. Rapid ingestion may cause air swallowing. If water is unsatisfactory, an unsweetened juice (avoid calories) may improve palatability. A heavy or pulpy juice may minimize complaints relative to consistency. Fluid and fiber intake (the latter may also produce some additional cholesterol lowering effect) should be

increased to alleviate constipation. Laxatives should not be used, but stool softeners may be indicated occasionally.

- Nicotinic acid: discuss flushing, its expected duration, development of tolerance, and the need to avoid taking medication on an empty stomach. Flushing may be diminished initially by pretreatment with an inhibitor of prostaglandin synthesis or use of a variety of sustained-release preparations such as Nico-Bid. Note that the cost of the sustained-release preparations is much greater than that of the usual nicotinic acid tablets.
- Identify the most likely side effects and ways the patient has handled such symptoms in the past. Identify ways the patient can manage these side effects should they occur. It is important to reinforce the patient's capability to manage these symptoms if they do occur.
- Review the patient's daily routine both during the week and on weekends. Help the patient to identify lifestyle factors that might interfere with adherence, and to identify ways in which the regimen or the daily routine could be adjusted to enhance adherence.
- Teach the patient how to maintain a daily record of medication intake as well as how to use that record to identify factors, if any, which contribute to missed medication doses or to self-adjustments to the medication dosage.
- Teach the patient about cholesterol-adherence relationships. In particular, stress the variability that exists in measured cholesterol values due to both laboratory and biological factors (e.g., measurement methods, laboratory variation, seasonal variability, weight change, dietary intake, and stress).

3. *Initiation of Treatment.*

- Tailor drug regimen to patient characteristics rather than asking for lifestyle changes in addition to those already prescribed.
- Establish a regular follow-up schedule that will allow for the early identification and remediation of any problems. If possible, supplement the regular visit schedule with between-visit telephone checks until the regimen is solidly in place.
- Gradually build up to the prescribed dose to minimize the occurrence of side effects and to allow the patient to adjust to the regimen.
- Introduce self-monitoring and review these records at follow-up appointments until the patient is consistently adhering to the medication regimen at full dosage. Assist with any adherence difficulties promptly.

4. *Ongoing Maintenance of Adherence.*

- Provide regular feedback to the patient regarding his or her cholesterol level so that the patient is aware of the treatment's success, and thus, the importance of adherence.

- Involve spouses or other family members in the patient's therapy. Social support has a strong influence on long-term adherence.
- Request that the patient periodically self-monitor adherence to the medication regimen. Use these records to evaluate the patient's adherence and to identify any difficulties the patient may be experiencing.
- Maintain regularly scheduled followup with the patient, with active pursuit after missed appointments. Regular supervision is an important factor in maintaining adherence.
- Give prompt attention to any changes in treatment response or in adherence.
- Increase attention and the frequency of follow-up visits or telephone contact during periods of life stress or life change to minimize the adherence problems that are likely to ensue.
- Encourage self-monitoring during periods of stress or life change to help the patient maintain awareness of the medication regimen and to identify problems that may be arising.
- Teach the patient to solve problems. The ability to manage everyday therapy problems helps remove barriers to effective treatment.

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